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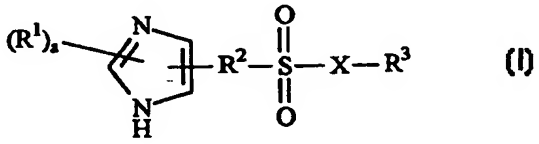

(I)

(57) Abstract

Compounds of formula (I) wherein R^1 is selected from C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 alkylthio, carboxy, carboxy (C_1 to C_6)alkyl, formyl, C_1 to C_6 alkylcarbonyl, C_1 to C_6 alkylcarbonylalkoxy, nitro, trihalomethyl, hydroxy, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, aryl, C_1 to C_6 alkylaryl, halo, sulfamoyl and cyano; R^2 is C_1 to C_{20} hydrocarbylene, in which one or more hydrogen atoms may be replaced by halogen atoms and up to 6 carbon atoms may be replaced by oxygen, nitrogen or sulfur atoms, provided that R^2 does not contain a –O–O– group, and provided also that the atom in R^2 which is linked to the $-SO_2-$ moiety is a carbon atom; R^3 is hydrogen or C_1 to C_{15} hydrocarbyl, in which one or more hydrogen atoms may be replaced by halogen atoms and up to 3 carbon atoms may be replaced by oxygen, nitrogen or sulfur atoms, provided that R^3 does not contain a –O–O– group; X is a bond or $-NR^4-$, wherein R^4 is hydrogen or non–aromatic C_1 to C_5 hydrocarbyl (in which one or more hydrogen atoms may be replaced by halogen atoms and up to 2 carbon atoms may be replaced by oxygen, nitrogen or sulfur atoms, provided that R^4 does not contain a –O–O– group), aryl(C_1 to C_3)alkyl or R^4 represents a bond to R^2; and a is from 0 to 2, and their pharmaceutically acceptable salts are useful as histamine H_3 receptor ligands.

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1H–4(5)–SUBSTITUTED IMIDAZOLE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS HISTAMINE H_3 RECEPTOR LIGANDS

This invention relates to compounds which bind to histamine H_3 receptors, and to methods of making such compounds.

Histamine is well known as a mediator in certain hypersensitive reactions of the body, such as allergic rashes, hayfever and asthma. These conditions are now commonly treated with potent antagonists of histamine, so-called "antihistamines".

In the 1940s, it was noted that some physiological effects of histamine, such as increased gastric acid secretion and cardiac stimulation, were not blocked by the antihistamines which were then available. This led to the proposal that histamine receptors exist in at least two distinct types, referred to as H_1 and H_2 receptors. Subsequently, H_2 antagonists (such as cimetidine, ranitidine and famotidine) were identified, and they have become important in the treatment of gastric ulcers.

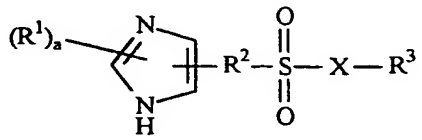
In the early 1980s, it was established that histamine also has a role as a neurotransmitter in the central nervous system. Arrang *et al.*, Nature 302, 832 to 837 (1983), proposed the existence of a third histamine receptor subtype (H_3) located presynaptically on histaminergic nerve endings. Arrang *et al.* postulated that the H_3 receptor is involved in inhibiting the synthesis and release of histamine in a negative feedback mechanism. The existence of the H_3 receptor was subsequently confirmed by the development of selective H_3 agonists and antagonists (Arrang *et al.*, Nature 327, 117 to 123 (1987)). The H_3 receptor has subsequently been shown to regulate the release of other neurotransmitters both in the central nervous system and in peripheral organs, in particular in the lungs and GI tract. In addition, H_3 receptors are reported to regulate the release of histamine from mast cells and enterochromaffin-like cells.

A need exists for potent and selective H_3 ligands (both agonists and antagonists) as tools in the study of the role of histamine as a neurotransmitter, and in its roles as a neuro-, endo- and paracrine hormone. It has also been anticipated that H_3 ligands will have

therapeutic utility for a number of indications including use as sedatives, sleep regulators, anticonvulsants, regulators of hypothalamo-hypophyseal secretion, antidepressants and modulators of cerebral circulation, and in the treatment of asthma and irritable bowel syndrome.

A number of imidazole derivatives have been proposed in the patent literature as H_3 ligands. Representative are the disclosures of EP-A-0197840, EP-A-0214058, EP-A-0458661, EP-A-0494010, EP-A-0531219, WO91/17146, WO92/15567, WO93/01812, WO93/12093, WO93/12107, WO93/12108, WO93/14070, WO93/20061, WO94/17058, WO95/06037, WO95/11894, WO95/14007, US-A-4988689 and US-A-5217986.

According to the present invention, there is provided a compound of the formula



I

wherein R^1 is selected from C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 alkylthio, carboxy, carboxy(C_1 to C_6)alkyl, formyl, C_1 to C_6 alkylcarbonyl, C_1 to C_6 alkylcarbonylalkoxy, nitro, trihalomethyl, hydroxy, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, aryl, C_1 to C_6 alkylaryl, halo, sulfamoyl and cyano;

R^2 is C_1 to C_{20} hydrocarbylene, in which one or more hydrogen atoms may be replaced by halogen atoms and up to 6 carbon atoms may be replaced by oxygen, nitrogen or sulfur atoms, provided that R^2 does not contain a -O-O- group, and provided also that the atom in R^2 which is linked to the $-SO_2-$ moiety is a carbon atom;

R^3 is hydrogen or C_1 to C_{15} hydrocarbyl, in which one or more hydrogen atoms may be replaced by halogen atoms and up to 3 carbon atoms may be replaced by oxygen, nitrogen or sulfur atoms, provided that R^3 does not contain a -O-O- group;

X is a bond or $-NR^4-$, wherein R^4 is hydrogen or non-aromatic C_1 to C_5 hydrocarbyl (in which one or more hydrogen atoms may be replaced by

halogen atoms and up to 2 carbon atoms may be replaced by oxygen, nitrogen or sulfur atoms, provided that R^4 does not contain a -O-O- group), aryl(C_1 to C_3)alkyl or R^4 represents a bond to R^2; and
a is from 0 to 2 (preferably 0),

and pharmaceutically acceptable salts thereof.

R^2 is preferably C_1 to C_{15} hydrocarbylene, in which one or more hydrogen atoms may be replaced by halogen atoms and up to 4 carbon atoms may be replaced by oxygen, nitrogen or sulfur atoms, provided that R^2 does not contain a -O-O- group. More preferably, R^2 is C_1 to C_8 alkylene or alkenylene, optionally substituted by a hydroxyl group or an oxo group.

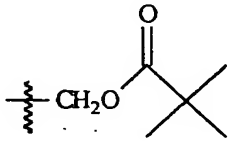
R^3 is preferably hydrogen, cycloalkyl(C_1 to C_3)alkyl or aryl(C_1 to C_3)alkyl. More preferably, R^3 is cyclohexyl(C_1 to C_3)alkyl, adamantyl(C_1 to C_3)alkyl, or phenyl(C_1 to C_3)alkyl in which the phenyl group is optionally substituted by halo or methyl.

R^4 is preferably hydrogen or C_1 to C_5 alkyl. When R^4 represents a bond to R^2, it preferably forms a five- or six-membered ring, which may be fused to a ring system within R^2. For example, the moiety $-R^2-SO_2-NR^4-$ may be an isothiazole dioxide group fused to six-membered carbocyclic ring. In the embodiment of Example 41 below, the moiety $-R^2-SO_2-NR^4-$ is a 2,3,3a,4,5,7a-hexahydro-benzo[d]isothiazole 1,1-dioxide group.

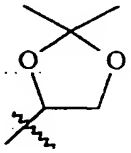
The invention also comprehends derivative compounds ("pro-drugs") which are degraded *in vivo* to yield the species of formula (I). Pro-drugs are usually (but not always) of lower potency at the target receptor than the species to which they are degraded. Pro-drugs are particularly useful when the desired species has chemical or physical properties which make its administration difficult or inefficient. For example, the desired species may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion of pro-drugs

may be found in Stella, V. J. *et al.*, "Prodrugs", Drug Delivery Systems, pp. 112-176 (1985), and Drugs, 29, pp.455-473 (1985).

Pro-drug forms of the pharmacologically-active compounds of the invention will generally be compounds according to formula (I) having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the form -$COOR^5$, wherein R^5 is C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl, substituted benzyl, or one of the following:



or



Amidated acid groups include groups of the formula -$CONR^6R^7$, wherein R^6 is H, C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl, or substituted benzyl, and R^7 is -OH or one of the groups just recited for R^6.

Compounds of formula (I) having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This will hydrolyse with first order kinetics in aqueous solution.

Pharmaceutically acceptable salts of the acidic compounds of the invention include salts with inorganic cations such as sodium, potassium, calcium, magnesium, and zinc, and salts with organic bases. Suitable organic bases include N-methyl-D-glucamine, benzathine, diolamine, olamine, procaine and tromethamine.

Pharmaceutically acceptable salts of the basic compounds of the invention include salts derived from organic or inorganic acids. Suitable anions include acetate, adipate, besylate, bromide, camsylate, chloride, citrate, edisylate, estolate, fumarate, gluceptate,

gluconate, glucuronate, hippurate, hyclate, hydrobromide, hydrochloride. iodide, isethionate, lactate, lactobionate, maleate, mesylate, methylbromide, methylsulfate, napsylate, nitrate, oleate, pamoate, phosphate, polygalacturonate, stearate, succinate, sulfate, sulfosalicylate, tannate, tartrate, terephthalate, tosylate and triethiodide.

The compounds of the invention may exist in various enantiomeric, diastereomeric and tautomeric forms. It will be understood that the invention comprehends the different enantiomers, diastereomers and tautomers in isolation from each other, as well as mixtures of enantiomers, diastereomers and tautomers.

The term "hydrocarbyl", as used herein, refers to monovalent groups consisting of carbon and hydrogen. Hydrocarbyl groups thus include alkyl, alkenyl, and alkynyl groups (in both straight and branched chain forms), cycloalkyl (including polycycloalkyl), cycloalkenyl, and aryl groups, and combinations of the foregoing, such as alkylaryl, alkenylaryl, alkynylaryl, cycloalkylaryl, and cycloalkenylaryl groups. The term "hydrocarbylene" refers to corresponding divalent groups, the two free valencies being on separate atoms.

When reference is made herein to a carbon atom of a hydrocarbyl group being replaced by O, S or N, it will be understood that what is meant is that a $-CH_2-$ group is replaced by –O- or –S-, or that $-\overset{|}{C}H-$ is replaced by $-\overset{|}{N}-$.

A "carbocyclic" group, as the term is used herein, comprises one or more closed chains or rings, which consist entirely of carbon atoms, and which may be substituted. Included in such groups are alicyclic groups (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and adamantyl), groups containing both alkyl and cycloalkyl moieties (such as adamantanemethyl), and aromatic groups (such as phenyl, naphthyl, indanyl, fluorenyl, (1,2,3,4)-tetrahydronaphthyl, indenyl and isoindenyl).

The term "aryl" is used herein to refer to aromatic carbocyclic groups, including those mentioned above, which may be substituted.

A "heterocyclic" group comprises one or more closed chains or rings which have at least one atom other than carbon in the closed chain or ring, and which may be substituted. Examples include benzimidazolyl, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl.

When reference is made herein to a substituted carbocyclic group (such as substituted phenyl) or a substituted heterocyclic group, the substituents are preferably from 1 to 3 in number and selected from C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 alkylthio, carboxy, carboxy(C_1 to C_6)alkyl, formyl, C_1 to C_6 alkylcarbonyl, C_1 to C_6 alkylcarbonylalkoxy, nitro, trihalomethyl, hydroxy, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, halo, sulfamoyl and cyano.

The term "halogen", as used herein, refers to any of fluorine, chlorine, bromine and iodine.

We have found that a number of compounds in the prior art have shown a significant discrepancy in their activity as measured by two ileum based assays which are described below. We would interpret discrepancies between the functional and binding assays of greater than about 0.5 log units as significant. Analysis of data obtained in these particular functional and radioligand binding assays and also in other related bioassays suggests that the discrepancy may be connected, at least in part, with residual efficacy inherent in these structures. In practice, this means that these particular compounds may act as agonists, at least in some tissues.

Surprisingly, we have found that the compounds disclosed herein do not show a significant discrepancy in the two assays. Thus, these compounds may be considered to have minimal potential to express agonist action, and would be expected to behave as antagonists or, at constitutively-active receptors, as inverse agonists. In one aspect, therefore, the present invention provides the use of these compounds as histamine antagonists or inverse agonists, and in the manufacture of medicaments for this purpose.

Pharmaceutically acceptable salts of the acidic or basic compounds of the invention can of course be made by conventional procedures, such as by reacting the free base or acid with at least a stoichiometric amount of the desired salt-forming acid or base.

It is anticipated that the compounds of the invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical administration, and inhalation.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

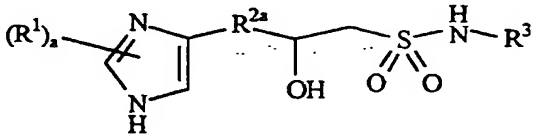
Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

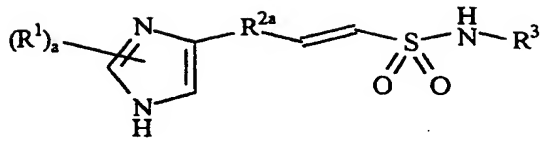
For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

Effective doses of the compounds of the present invention may be ascertained by conventional methods. The specific dosage level required for any particular patient will depend on a number of factors, including the severity of the condition being treated, the route of administration and the weight of the patient. In general, however, it is anticipated that the daily dose (whether administered as a single dose or as divided doses) will be in the range 0.001 to 5000 mg per day, more usually from 1 to 1000 mg per day, and most usually from 10 to 200 mg per day. Expressed as dosage per unit body weight, a typical dose will be expected to be between 0.01 μg/kg and 50 mg/kg, especially between 10 μg/kg and 10 mg/kg, e.g. between 100 μg/kg and 2 mg/kg.

Compounds according to Formula I in which X is -NH- can conveniently be prepared via the key intermediates 2a and 2b (Figure 1), using the existing methods of Tozer[5] and Thompson[6]. In Figure 1, Z is H or a Boc group or other suitable migrating group, Z^1 is a protecting group, Z^2 is H or a further protecting group, and R^{2a} is C_1 to C_{18} hydrocarbylene. Compound 2b may also be obtained from compound 2a when Z is other than H by treatment with a base such as caesium carbonate. Compound 2a may be deprotected e.g. with trifluoroacetic acid to yield a compound of the formula

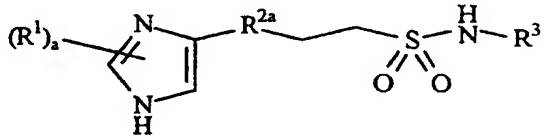


If compound 2b is deprotected under appropriate conditions, the result is a compound of the formula

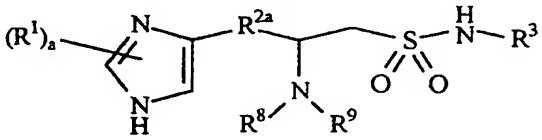


(II)

If compound 2b is reduced (e.g. by hydrogenation over a palladium/charcoal catalyst), and then deprotected, the result is a compound of formula



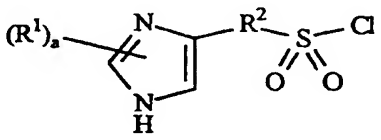
If compound 2b is allowed to react with an amine R^8R^9NH and deprotected, then a compound of the formula



is produced. This route is shown in Figure 2. R^8 and R^9 are independently H, lower (eg C_1 to C_5) alkyl, or are linked to each other to form an N-containing ring.

Compound (1) in Figure 1 may be prepared by conventional methods, such as by reaction of mesyl chloride with a compound of formula R^3NH_2 in the presence of a base such as triethylamine. If Z is other than H, the methanesulfonamide R^3NHSO_2Me may be treated with suitable reagents for protection (e.g. Boc_2O, catalytic DMAP) to give compound (1).

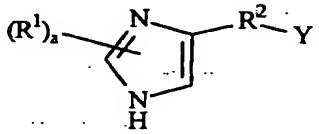
Compounds of Formula I in which X is -NH- may also be prepared by reacting a compound of formula



with a compound of formula R^3NH_2 in the presence of a base.

When X is $-NR^4-$ and R^4 is other than H, the R^4 group may be introduced by chemistry on late-stage protected intermediates well known to those skilled in the art.

Compounds of Formula I in which X represents a bond may be obtained by reacting a suitably protected compound of formula



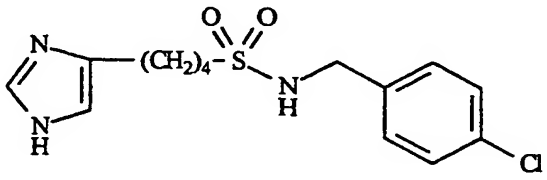
(wherein Y represents a leaving group such as bromide) with a compound of formula R^3SH, followed by oxidation of the resulting thioether to yield the desired sulfone. Protection of the imidazole ring may conveniently be by means of the procedure described in Example 23 below. Oxidation of the thioether can be achieved using a suitable oxidising agent such as Oxone®.

Compounds of Formula I in which X represents $-NR^4-$ and R^4 represents a bond to R^2 may be prepared by methods analogous to that illustrated in Figure 3. Compound (3) in Figure 3 is a suitably N-protected derivative of the compound of Formula II above in which R^{2a} is $-CH=CH-$. This compound is treated with sodium hydride, and then with allyl bromide, to form the N-allyl derivative (4). Ring closure is then effected by heating under pressure in a suitable dry solvent such as toluene.

The invention is now further illustrated by means of the following examples. All reactions were performed under an atmosphere of dried argon unless otherwise stated. Dichloromethane (DCM) was freshly distilled from calcium hydride. Tetrahydrofuran (THF) was freshly distilled from sodium–benzophenone ketyl.

Example 1

N-(4-Chlorobenzyl)-4-(1H-imidazol-4-yl)-1-butanesulfonamide



Step a. *N-(4-chlorobenzyl)-methanesulfonamide.* A solution of 4-chlorobenzylamine (12.20g, 86.2mmol) and triethylamine (14.4ml, 103mmol) in DCM (200ml) was cooled

in an ice bath. Mesyl chloride (7.34ml, 94.9mmol) was added dropwise and the solution was stirred for 10min. The cold bath was removed and the solution stirred for a further 2h. The reaction was diluted with an equal volume of DCM and washed with 10% citric acid solution and brine. The solvent was evaporated and the residue recrystallised from hot ethyl acetate. The product was thus obtained as a colourless crystalline solid (15.3g, 81%).

Step b. N-*(*tert-*butoxycarbonyl)*-N-*(4-chlorobenzyl)-methanesulfonamide.* To a solution of the product from step a (15.30g, 69.6mmol) and di-*tert*-butyl-dicarbonate (18.27g, 83.6mmol) in DCM (150ml) was carefully added *N,N*-dimethylaminopyridine (848mg, 6.96mmol); there was immediate and vigorous effervescence. The solution was stirred for 30min, by which time effervescence had ceased. The solution was diluted to a total volume of 500ml with DCM and washed twice with 10% citric acid solution and then brine. The solvent was evaporated to give yellow solid which was recrystallised from hot propan-2-ol (100ml). The precipitate was collected by filtration and dried in vacuo at 50°C to afford the product as a colourless crystalline solid (19.70g, 89%).

Step c. *3-[1-(triphenylmethyl)imidazol-4-yl]propanal.* A solution of oxalyl chloride (1.75ml, 20.1mmol) in DCM (60ml) was cooled to –78°C and dimethylsulfoxide (2.85ml, 20.1mmol) was added dropwise, with concomitant effervescence. The solution was stirred for 5min, by which time effervescence had ceased, and a solution of 3-[1-(triphenylmethyl)imidazol-4-yl]propan-1-ol (6.17g, 16.7mmol)[1] in DCM (30ml) was added by means of a cannula. The solution was stirred for 20min, triethylamine (8.40ml, 60.2mmol) was added, the cold bath was removed and the resultant solution stirred for 3h. A column of silica was flushed with an equal volume of ethyl acetate. The reaction mixture was applied to the top of the column and the column eluted to dryness. This was repeated with a column's volume of DCM to ensure complete removal of dimethylsulfide. The column was eluted with ethyl acetate and the aldehyde collected in fractions. The combined fractions were evaporated to give the product as a white solid (4.94g, 81%).

Step d. tert-*butyl (1-((((4-chlorobenzyl)amino)sulfonyl)methyl)-3-(1-(triphenylmethyl) imidazol-4-yl)propyl) carbonate*. A solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-chlorobenzyl)-methanesulfonamide (step b) (204mg, 0.64mmol) in THF (2.5ml) was cooled to –78°C, 1.5M lithium diisopropylamide (430µl, 0.64mmol) was added dropwise and the solution was stirred for 30min. A solution of the aldehyde from step c of this example (194mg, 0.53mmol) was added by means of a cannula, the cold bath was removed and the solution was stirred for 2h. The reaction mixture was quenched with saturated ammonium chloride solution (10ml) and extracted with diethyl ether (2x10ml). The combined extracts were washed with brine, dried over sodium sulfate, filtered and the solvent evaporated. Flash column chromatography (silica, ethyl acetate) of the residue gave the product (R_f 0.5) as a colourless foam (146mg, 40%): ^{1}H NMR (300MHz, $CDCl_3$) 7.33(10H, m), 7.25(4H, m), 7.10(6H, m), 6.55(1H, s), 6.13(1H, t), 5.15(1H, m), 4.25(2H, d), 3.40(1H, dd), 3.16(1H, dd), 2.62(2H, m), 2.18(2H, m), 1.96(2H, m), 1.45(9H, s).

Step e. *(E)*-N-*(4-chlorobenzyl)-4-(1-(triphenylmethyl)imidazol-4-yl)-1-but-1-enesulfonamide*. To a solution of the product from the previous step (146mg, 0.21mmol) in anhydrous methanol (3ml) was added cesium carbonate (140mg, 0.42mmol). The mixture was stirred overnight and the solvent evaporated. The residue was purified by flash column chromatography (silica, ethyl acetate) and gave the product (R_f 0.3) as a colourless foam (85mg, 72%): ^{1}H NMR (300MHz, $CDCl_3$) 7.33(10H, m), 7.30(2H, d), 7.21(2H, d), 7.12(6H, m), 6.77(1H, dt, J=15, 7Hz), 6.55(1H, d), 6.15(1H, J=15, 1.5Hz), 4.61(1H, t), 4.14(2H, d), 2.67(2H, m), 2.58(2H, m).

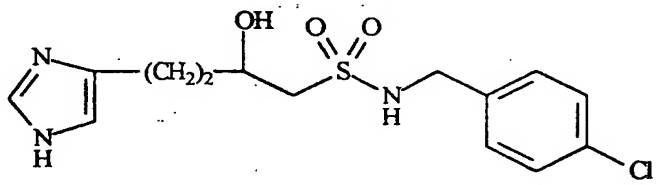
Step f. N-*(4-chlorobenzyl)-4-(1-(triphenylmethyl)imidazol-4-yl)-1-butanesulfonamide*. A round bottom flask containing the product from the previous step (282mg, 0.50mmol), 10% palladium-on-charcoal (34mg) and THF (10ml) was evacuated and flushed with hydrogen three times. The mixture was vigorously stirred overnight under an atmosphere of hydrogen. The catalyst was removed by filtration and the filtrate evaporated. The residue was purified by flash column chromatography (silica, ethyl acetate) and gave the product (R_f 0.3) as a colourless foam (190mg, 67%): ^{1}H NMR

(300MHz, $CDCl_3$) 7.32(10H, m), 7.27(4H, m), 7.12(6H, m), 6.53(1H, d), 5.45(1H, m), 4.23(2H, d), 2.97(2H, t), 2.53(2H, t), 1.79(4H, m).

Step g. Trifluoroacetic acid (3ml) was added to the product from the previous step (190mg, 0.33mmol). The flask was stoppered and the resultant yellow solution left to stand overnight under ambient conditions. The solvent was evaporated and the residue purified by flash column chromatography (silica; 1:10:90 ammonia(880)/methanol/dichloromethane). Thus, the title compound (R_f 0.3) was isolated as a colourless oil (76mg, 70%): ^{1}H NMR (300MHz, *d4*-MeOH) 7.57(1H, s), 7.34(4H, s), 6.79(1H, d), 4.19(2H, s), 2.97(2H, t), 2.58(2H, t), 1.72(4H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 48.95, H 5.00, N 9.47%; $C_{18}H_{22}ClN_3O_6S$ requires: C 48.70, H 5.00, N 9.47%.

Example 2

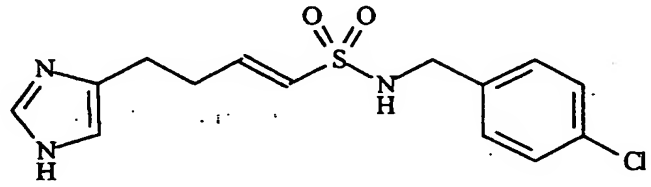
N-(4-Chlorobenzyl)-2-hydroxy-4-(1H-imidazol-4-yl)-1-butanesulfonamide



tert-Butyl (1-((((4-chlorobenzyl)amino)sulfonyl)methyl)-3-(1-(triphenylmethyl)imidazol-4-yl)propyl) carbonate (Example 1, step d) (137mg, 0.20mmol) was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.15, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a white solid (56mg, 70%): ^{1}H NMR (300MHz, *d4*-MeOH) 7.57(1H, d), 7.34(4H, s), 6.81(1H, d), 4.22(2H, s), 4.08(1H, m), 3.15(2H, m), 2.70(2H, m), 1.85(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 46.85, H 5.06, N 8.86%; $C_{18}H_{22}ClN_3O_7S$ requires: C 47.01, H 4.82, N 9.14%.

Example 3

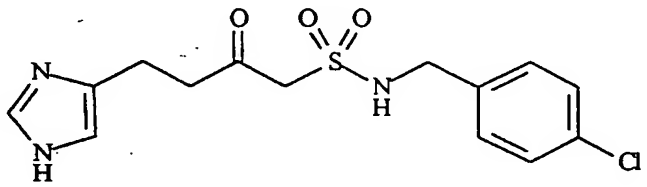
(E)-N-(4-Chlorobenzyl)-4-(1H-imidazol-4-yl)-1-but-1-enesulfonamide



(E)-N-(4-Chlorobenzyl)-4-(1-(triphenylmethyl)imidazol-4-yl)-1-but-1-enesulfonamide (Example 1, step e) (85mg, 0.15mmol) was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.25, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a white solid (39mg, 80%): ^{1}H NMR (300MHz, *d4*-MeOH) 7.60(1H, d), 7.31(4H, m), 6.84(1H, d), 6.65(1H, dt, J=15, 7Hz), 6.23(1H, dt, J=15, 1.5Hz); 3.99(2H, s), 2.74(2H, t), 2.57(2H, dd). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 48.64, H 4.74, N 9.46%; $C_{18}H_{20}ClN_3O_6S$ requires: C 48.93, H 4.56, N 9.51%.

Example 4

N-*(4-Chlorobenzyl)-2-oxy-4-(1H-imidazol-4-yl)-1-butanesulfonamide*



Step a. N-*(4-chlorobenzyl)-2-hydroxy-4-(1-(triphenylmethyl)imidazol-4-yl)-1-butanesulfonamide*. A solution of *N*-(4-chlorobenzyl)-methanesulfonamide (Example 1, step a) (314mg, 1.43mmol) in THF (4.5ml) was cooled to –78°C, 1.5M lithium diisopropylamide (1.95ml, 2.93mmol) was added dropwise and the solution was stirred for 30 min. A solution of 3-[1-(triphenylmethyl)imidazol-4-yl]propanal (Example 1, step c) (314mg, 1.30mmol) was added by means of cannula, the cold bath was removed and the solution was stirred overnight. The reaction mixture was quenched with saturated ammonium chloride solution (20ml) and extracted with diethyl ether (2x20ml). The combined extracts were washed with brine, dried over sodium sulfate,

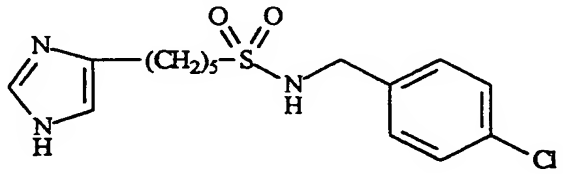
filtered and the solvent evaporated. Flash column chromatography (silica, ethyl acetate) of the residue gave the product (R_f 0.2) as a colourless oil (313mg, 37%): ^{1}H NMR (300MHz, $CDCl_3$) 7.34(10H, m), 7.29(4H, m), 7.13(6H, m), 6.58(1H, s), 5.42(1H, t), 4.34(1H, m), 4.26(2H, m), 3.22(1H, dd), 3.07(1H, dd), 2.75(2H, m), 1.84(2H, m).

Step b. *N-(4-chlorobenzyl)-2-oxy-4-(1-(triphenylmethyl)imidazol-4-yl)-1-butanesulfonamide.* The hydroxy compound produced in the previous step was oxidised and purified using the procedure of Example 1, step c. The ketone product (R_f 0.4, ethyl acetate) was thereby isolated as a colourless oil (195mg, 68%): ^{1}H NMR (300MHz, $CDCl_3$) 8.10(1H, t), 7.33(10H, m), 7.21(2H, d), 7.15(2H, d), 7.04(6H, m), 6.52(1H, s), 4.22(2H, d), 4.21(2H, s), 3.12(2H, t), 2.91(2H, t).

Step c. The product from the previous step (190mg, 0.33mmol) was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.20, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a white solid (90mg, 80%). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan: ^{1}H NMR (300MHz, *d6*-DMSO) 8.77(1H, s), 8.00(1H, t), 7.40(2H, d), 7.34(2H, d), 7.28(1H, s), 6.03(2H, s), 4.30(2H, s), 4.15(2H, d), 3.04(2H, t), 2.82(2H, t). Found: C 46.47, H 4.64, N 9.05%; $C_{18}H_{20}ClN_3O_7S.0.45H_2O$ requires: C 46.39, H 4.52, N 9.02%.

Example 5

N-(4-Chlorobenzyl)-5-(1H-imidazol-4-yl)-1-pentanesulfonamide



Step a. *(Z)-4-[4-(1,3-dioxolan-2-yl)but-2-enyl]-1-(triphenylmethyl)-imidazole.* A suspension of [2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide (48.5g, 109mmol) in tetrahydrofuran (500ml) was cooled to –20°C. 1.6M *n*-Butyl lithium (68.3ml, 109mmol) was added dropwise and the solution stirred for 1h. A solution of

[1-(triphenylmethyl)imidazol-4-yl]carbaldehyde[2] (36.8g, 109mmol) in tetrahydrofuran (500ml) was added slowly and the reaction mixture stirred at room temperature for 18h. The reaction mixture was concentrated in vacuo, water was added and the mixture filtered through a pad of Celite. The filtrate was extracted with dichloromethane (2x500ml) and the combined extracts dried over magnesium sulfate. Filtration and evaporation gave a yellow oil. From flash column chromatography (silica; 10-20% ethyl acetate/hexane) the product was isolated as a yellow oil (19.7g, 42%).

Step b. *4-[4-(1,3-dioxolan-2-yl)butyl]-1-(triphenylmethyl)-imidazole.* A solution of the product from step a in ethanol was hydrogenated in the presence of a catalytic quantity of 10% palladium-on-charcoal at atmospheric pressure and temperature for 18h. The product was isolated as a colourless oil in quantitative yield.

Step c. *4-[1-(triphenylmethyl)imidazol-4-yl]butanal.* A suspension of the product from step b (19.8g, 46.6mmol) in a mixture of acetone (300ml) and 2M hydrochloric acid (50ml) was stirred at room temperature for 20h. The mixture was neutralised with sodium hydrogen carbonate, filtered and the filtrate extracted with dichloromethane (3x100ml). The combined extracts were dried over magnesium sulfate, filtered and evaporated to give the product as a colourless oil (16.1g, 91%).

Step d. tert-*butyl (1-((((4-chlorobenzyl)amino)sulfonyl)methyl)-4-(1-(triphenylmethyl) imidazol-4-yl)butyl) carbonate.* A solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-chlorobenzyl)-methanesulfonamide (Example 1, step b) (1.53g, 4.80mmol) in THF (16ml) was cooled to –78°C, 1.5M lithium diisopropylamide (3.20ml, 4.80mmol) was added dropwise and the solution was stirred for 1h. A solution of the aldehyde from step c of this example (1.83g, 4.80mmol) in THF(16ml) was added by means of a cannula, the cold bath was removed and the solution was stirred for 2h. The reaction was quenched with saturated ammonium chloride solution (20ml) and the mixture was extracted with ethyl acetate (2x20ml). The combined extracts were washed with brine, dried over sodium sulfate, filtered and the solvent evaporated. Flash column chromatography (silica, 50% ethyl acetate/toluene) of the residue gave the product (R_f 0.4) as a colourless oil (1.60g, 48%): ^{1}H NMR (300MHz, $CDCl_3$) 7.33(10H, m),

7.22(4H, m), 7.10(6H, m), 6.52(1H, d), 6.47(1H, t), 5.11(1H, m), 4.26(2H, d), 3.38(1H, dd), 3.11(1H, dd), 2.55(2H, t), 1.87(1H, m), 1.68(3H, m), 1.47(9H, s).

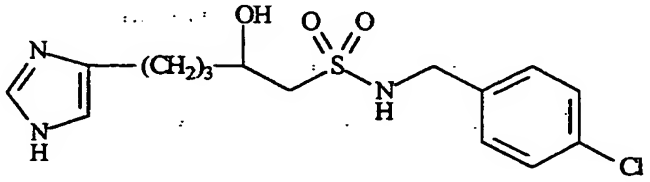
Step e. *(E)-N-(4-chlorobenzyl)-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pent-1-enesulfonamide.* The elimination reaction on the product from the previous step (1.60g, 2.29mmol) was performed according to the procedure of Example 1, step e. The vinylsulfonamide product (R_f 0.5, ethyl acetate) was thus obtained as a white solid (1.20g, 91%): ^{1}H NMR (300MHz, $CDCl_3$) 7.33(10H, m), 7.26(4H, m), 7.14(6H, m), 6.77(1H, dt, J=15,7Hz), 6.53(1H, d), 6.11(1H, d, J=15Hz), 4.66(1H, t), 4.14(2H, d), 2.56(2H, d), 2.23(2H, dd), 1.79(2H, quint.).

Step f. N-*(4-chlorobenzyl)-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pentanesulfonamide.* The hydrogenation of the product from the previous step was performed according to the procedure of Example 1, step f. The product (R_f 0.5, 0.5:5:95 ammonia(880)/methanol/dichloromethane) was thus obtained as a colourless oil: ^{1}H NMR (300MHz, $CDCl_3$) 7.33(10H, m), 7.28(4H, m), 7.12(6H, m), 6.52(1H, d), 5.45(1H, m), 4.24(2H, d), 2.96(2H, t), 2.53(2H, t), 1.81(2H, m), 1.63(2H, m), 1.46(2H, m).

Step g. The product from the previous step (148mg, 0.25mmol) was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.30, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a white solid (73mg, 84%): ^{1}H NMR (300MHz, *d4*-MeOH) 7.59(1H, d), 7.35(4H, m), 6.78(1H, s), 4.20(2H, s), 2.93(2H, t), 2.58(2H, t), 1.74(2H, quin.), 1.62(2H, quin.), 1.39(2H, quin.). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 49.70, H 5.24, N 9.18%; $C_{19}H_{24}ClN_3O_6S$ requires: C 49.83, H 5.28, N 9.18%.

Example 6

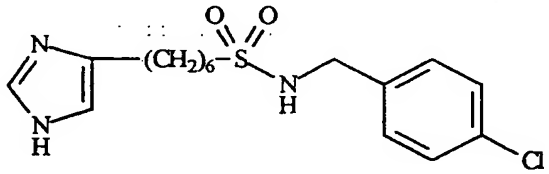
N-(4-Chlorobenzyl)-2-hydroxy-5-(1H-imidazol-4-yl)-1-pentanesulfonamide



tert-Butyl (1-((((4-chlorobenzyl)amino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate (Example 5, step d) was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.3, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a colourless oil: ^{1}H NMR (300MHz, d_4-MeOH) 7.56(1H, d), 7.35(4H, m), 6.78(1H, d), 4.22(2H, s), 4.08(1H, m), 3.10(2H, m), 2.60(2H, m), 1.75(2H, m), 1.53(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 47.78, H 5.27, N 8.61%; $C_{19}H_{24}ClN_3O_7S$ requires: C 48.15, H 5.10, N 8.87%.

Example 7

N-(4-Chlorobenzyl)-6-(1H-imidazol-4-yl)-1-hexanesulfonamide



Step a. *(E)-5-[1-(triphenylmethyl)-4-imidazolyl]-pent-2-enoate*. A suspension of sodium hydride (60% dispersion in oil) (1.43g, 36.0mmol) in THF (20ml) was cooled in an ice-bath and a solution of triethylphosphonoacetate (7.20ml, 35.6mmol) in THF (50ml) was added over 10min. The mixture was allowed to warm to room temperature, stirred for 20min and cooled to –20°C. A solution of 3-[1-(triphenylmethyl)imidazol-4-yl]propan-1-al (Example 1, step c) (10.60g, 28.9mmol) in THF (100ml) was added over 30min, the mixture allowed to warm to room temperature and stirring continued for 1.5h. The reaction mixture was diluted with ethyl acetate (150ml), washed 10% citric acid solution (2x150ml) and brine (2x150ml), and dried over sodium sulfate. Filtration and evaporation of the filtrate gave the product as a yellow oil in quantitative yield.

Step b. *5-[1-(triphenylmethyl)-4-imidazolyl]-pentanoate*. A round bottom flask containing the product from the previous step (12.6g, 29.0mmol), 10% palladium-on-charcoal (1.03g) and 1:10 methanol/THF (220ml) was evacuated and flushed with hydrogen three times. The mixture was vigorously stirred overnight under an atmosphere of hydrogen. The catalyst was removed by filtration and the filtrate evaporated. The residue was purified by flash column chromatography (silica, 30-60% ethyl acetate/DCM) and gave the product as a white solid (6.34g, 50%).

Step c. *5-[1-(triphenylmethyl)imidazol-4-yl]pentan-1-ol*. A suspension of lithium aluminium hydride (346mg, 9.1mmol) in THF (100ml) was cooled in an ice-bath and a solution of the product from the previous step (6.34g, 14.5mmol) in THF (50ml) was added over 30min. The mixture was stirred at room temperature for 2h and then at reflux for 3h. The mixture was allowed to cool to room temperature, 1.0M lithium aluminium hydride in diethyl ether (8ml, 8.0mmol) was added over 5min, and stirring continued for 18h. 50% Ethyl acetate/THF (60ml) was added dropwise followed by sodium sulfate decahydrate (10g). The resultant precipitate was removed by filtration and the filtrate evaporated to give a yellow oil, which solidified on standing. The solid was triturated with diethyl ether and collected by filtration (3.75g, 65%).

Step d. *5-[1-(triphenylmethyl)imidazol-4-yl]pentanal*. The hydroxy compound (1.60g, 4.04mmol) produced in the previous step was oxidised and purified using the procedure of Example 1, step c. The product (R_f 0.2, ethyl acetate) was thus obtained as a yellow oil (1.08g, 68%).

Step e. tert-*butyl (1-((((4-chlorobenzyl)amino)sulfonyl)methyl)-5-(1-(triphenylmethyl) imidazol-4-yl)pentyl) carbonate.* 5-[1-(Triphenylmethyl)imidazol-4-yl]pentanal (1.05g, 2.66mmol), from the previous step and *N*-(*tert*-butoxycarbonyl)-*N*-(4-chlorobenzyl)-methanesulfonamide (934mg, 2.92mmol) (Example 1, step b) were reacted together according to the procedure of Example 5, step d. The product (R_f 0.3, 50% ethyl acetate/toluene) was thus obtained as a colourless oil (722mg, 38%).

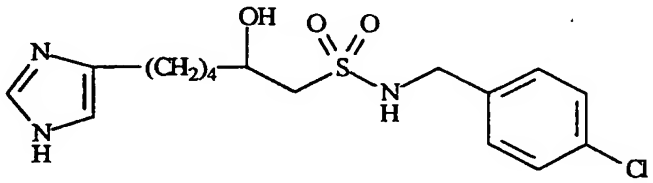
Step f. N-*(4-chlorobenzyl)-6-(1-(triphenylmethyl)imidazol-4-yl)-1-hex-1-enesulfonamide*. The elimination reaction on the product from the previous step (710mg, 0.99mmol) was performed according to the procedure of Example 1, step e. The vinylsulfonamide product (R_f 0.5, 50% ethyl acetate/toluene) was thus obtained as a colourless oil (452mg,77%).

Step g. N-*(4-chlorobenzyl)-6-(1-(triphenylmethyl)imidazol-4-yl)-1-hexane sulfonamide*. The hydrogenation of the product from the previous step (452mg, 0.76mmol) was performed according to the procedure of Example 1, step f. The product was thus obtained as a colourless oil (423mg, 93%).

Step h. The product from the previous step (420mg, 070mmol) was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.35, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a white solid (183mg, 77%): ^{1}H NMR (300MHz, *d4*-MeOH) 7.56(1H, d), 7.35(4H, m), 6.76(1H, s), 4.20(2H, s), 2.92(2H, m), 2.58(2H, t), 1.72(2H, m), 1.62(2H, m), 1.35(4H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 50.67, H 5.63, N 9.01%; $C_{20}H_{26}ClN_3O_6S$ requires: C 50.90, H 5.55, N 8.90%.

Example 8

N-(4-Chlorobenzyl)-2-hydroxy-6-(1H-imidazol-4-yl)-1-hexanesulfonamide

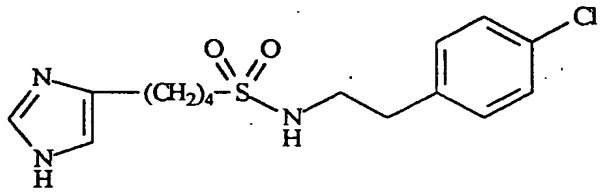


tert-Butyl (1-((((4-chlorobenzyl)amino)sulfonyl)methyl)-5-(1-(triphenylmethyl)imidazol-4-yl)pentyl) carbonate (194mg, 0.28mmol) (Example 7, step e) was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.2, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a colourless oil (80mg, 77%): ^{1}H NMR (300MHz, *d4*-MeOH) 7.56(1H, s), 7.35(4H,

m), 6.77(1H, s), 4.22(2H, s), 4.04(1H, m), 3.08(2H, m), 2.60(2H, m), 1.66(2H, m), 1.53(2H, m), 1.37(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 47.52, H 5.44, N 8.36%; $C_{20}H_{26}ClN_3O_7S$ requires: C 47.65, H 5.56, N 8.33%.

Example 9

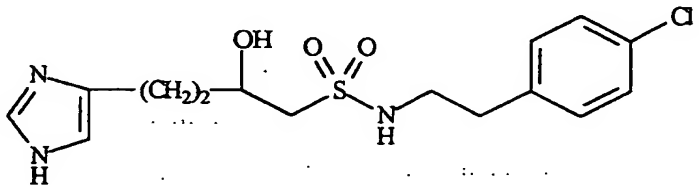
N-(4-Chlorophenethyl)-4-(1H-imidazol-4-yl)-1-butanesulfonamide



N-(*tert*-Butoxycarbonyl)-*N*-(4-chlorophenethyl)-methanesulfonamide was prepared from 4-chlorophenethylamine according to the procedure of Example 1, steps a and b. It was reacted with 3-[1-(triphenylmethyl)imidazol-4-yl]propan-1-al (Example 1, step c) according to the procedure of Example 5, step d to produce *tert*-butyl (1-((((4-chlorophenethyl)amino)sulfonyl)methyl)-3-(1-(triphenylmethyl)imidazol-4-yl)propyl) carbonate. This was converted to the title compound using the procedure of Example 1, steps e to g. Thus, the title compound (R_f 0.35) was isolated as a colourless oil. The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. ^{1}H NMR (300MHz, d_6-DMSO) 8.86(1H, s), 7.34(3H, m), 7.26(2H, m), 7.11(1H, t), 6.03(2H, s), 3.13(2H, dd), 2.94(2H, t), 2.73(2H, t), 2.62(2H, t), 1.61(4H, m). Found: C 49.66, H 5.33, N 9.19%; $C_{19}H_{24}ClN_3O_6S$ requires: C 49.83, H 5.28, N 9.18%.

Example 10

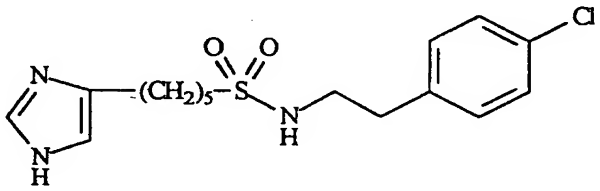
N-(4-Chlorophenethyl)-2-hydroxy-4-(1H-imidazol-4-yl)-1-butanesulfonamide



tert-Butyl (1-((((4-chlorophenethyl)amino)sulfonyl)methyl)-3-(1-(triphenylmethyl)imidazol-4-yl)propyl) carbonate (Example 9) was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.2, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a white solid: ^{1}H NMR (300MHz, *d4*-MeOH) 7.56(1H, d), 7.28(2H, dd), 7.22(2H, dd), 6.80(1H, d), 4.03(1H, m), 3.26(2H, m), 3.10(2H, m), 2.82(2H, t), 2.71(2H, m), 1.88(1H, m), 1.80(1H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan.

Example 11

N-(4-Chlorophenethyl)-5-(1H-imidazol-4-yl)-1-pentanesulfonamide

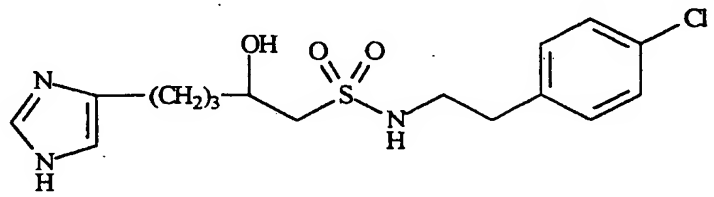


N-(*tert*-Butoxycarbonyl)-*N*-(4-chlorophenethyl)-methanesulfonamide was prepared from 4-chlorophenethylamine according to the procedure of Example 1, steps a and b. It was reacted with 4-[1-(triphenylmethyl)imidazol-4-yl]butanal (Example 5, step c) according to the procedure of Example 5, step d to produce *tert*-butyl (1-((((4-chlorophenethyl)amino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate. This was converted to the title compound using the procedure of Example 1, steps e to g. Thus, the title compound (R_f 0.3) was isolated as a colourless oil: ^{1}H NMR (300MHz, *d4*-MeOH) 7.55(1H, s), 7.28(2H, dt), 7.23(2H, dd), 6.77(1H, s), 4.03(1H, m), 3.27(2H, t), 2.88(2H, m), 2.83(2H, m), 2.58(2H, t), 1.65(4H, m), 1.42(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and

maleic acid in water/dioxan. Found: C 50.52, H 5.79, N 8.66%; $C_{20}H_{26}ClN_3O_6S$ requires: C 50.89, H 5.55, N 8.91%.

Example 12

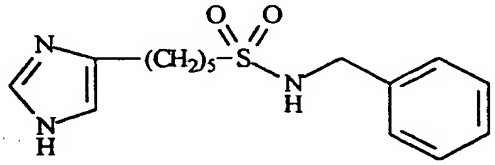
N-(4-Chlorophenethyl)-2-hydroxy-5-(1H-imidazol-4-yl)-1-pentanesulfonamide



tert-Butyl (1-((((4-chlorophenethyl)amino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate (Example 11) was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.15, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a colourless oil: ^{1}H NMR (300MHz, *d4*-MeOH) 7.56(1H, d), 7.28(2H, dd), 7.23(2H, d), 6.78(1H, s), 4.03(1H, m), 3.28(2H, m), 3.05(2H, m), 2.82(2H, t), 2.61(2H, m), 1.75(2H, m), 1.56(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan.

Example 13

N-Benzyl-5-(1H-imidazol-4-yl)-1-pentanesulfonamide

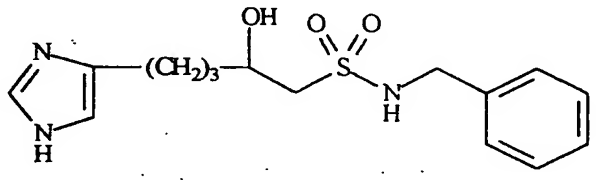


N-(*tert*-Butoxycarbonyl)-*N*-benzyl-methanesulfonamide was prepared from benzylamine essentially according to the procedure of Example 1, steps a and b. It was reacted with 4-[1-(triphenylmethyl)imidazol-4-yl]butanal (Example 5, step c) according to the procedure of Example 5, step d to produce *tert*-butyl (1-(((benzylamino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate. This was converted to the title compound using the procedure of Example 1, steps e to

g. Thus, the title compound (R_f 0.4) was isolated as a colourless oil: ^{1}H NMR (300MHz, *d4*-MeOH) 7.55(1H, s), 7.30(5H, m), 6.75(1H, s), 4.22(2H, s), 2.86(2H, t), 2.55(2H, t), 1.68(2H, quin.), 1.56(2H, quin.), 1.34(2H, quin.). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 53.87, H 6.03, N 10.03%; $C_{19}H_{25}N_3O_6S$ requires: C 53.89, H 5.95, N 9.92%.

Example 14

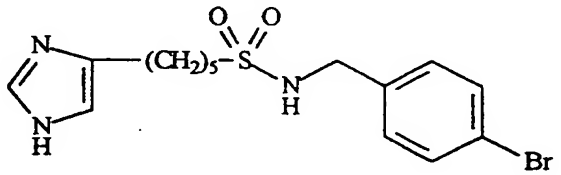
N-Benzyl-2-hydroxy-5-(1H-imidazol-4-yl)-1-pentanesulfonamide



tert-Butyl (1-(((benzylamino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate (Example 13) was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.15, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a colourless oil: ^{1}H NMR (300MHz, *d4*-MeOH) 7.57(1H, d), 7.30(5H, m), 6.78(1H, s), 4.24(2H, m), 4.03(1H, m), 3.04(2H, m), 2.59(2H, m), 1.71(2H, m), 1.52(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan.

Example 15

N-(4-Bromobenzyl)-5-(1H-imidazol-4-yl)-1-pentanesulfonamide

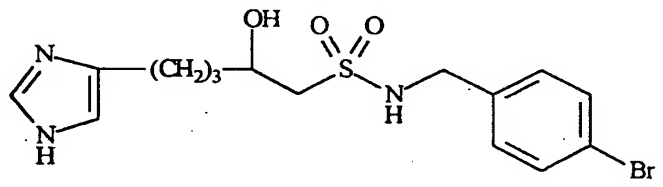


N-(*tert*-Butoxycarbonyl)-*N*-(4-bromobenzyl)-methanesulfonamide was prepared from (4-bromobenzyl)amine essentially according to the procedure of Example 1, steps a and b. It was reacted with 4-[1-(triphenylmethyl)imidazol-4-yl]butanal (Example 5, step c) according to the procedure of Example 5, step d to produce *tert*-butyl (1-((((4-

bromobenzyl)amino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate. This was converted to the title compound using the procedure of Example 1, steps e, f and g, with the modification to step f of the palladium catalyst being replaced by rhodium-on-alumina. Thus, the title compound (R_f 0.3, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a colourless oil: ^{1}H NMR (300MHz, *d4*-MeOH) 7.55(1H, s), 7.50(2H, d), 7.31(2H, d), 6.75(1H, s), 4.19(2H, s), 2.90(2H, t), 2.58(2H, t), 1.72(2H, quin.), 1.59(2H, quin.), 1.34(2H, quin.). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 45.51, H 4.85, N 8.28%; $C_{19}H_{24}BrN_3O_6S$ requires: C 45.42, H 4.82, N 8.36%.

Example 16

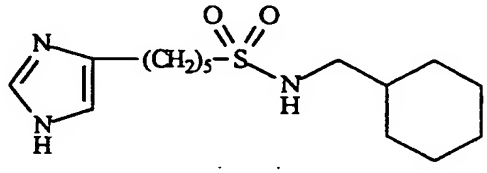
N-(4-Bromobenzyl)-2-hydroxy-5-(1H-imidazol-4-yl)-1-pentanesulfonamide



tert-Butyl (1-((((4-bromobenzyl)amino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate (Example 15) was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.2, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a colourless oil: ^{1}H NMR (300MHz, *d4*-MeOH) 7.56(1H, s), 7.49(2H, d), 7.30(2H, d), 6.78(1H, s), 4.20(2H, m), 4.07(1H, m), 3.10(2H, m), 2.60(2H, m), 1.71(2H, m), 1.55(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan.

Example 17

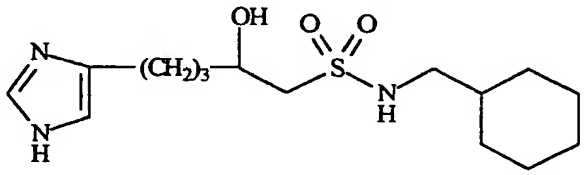
N-*Cyclohexylmethyl-5-(1H-imidazol-4-yl)-1-pentanesulfonamide*



N-(*tert*-Butoxycarbonyl)-*N*-cyclohexylmethyl-methanesulfonamide was prepared from cyclohexylmethyl amine essentially according to the procedure of Example 1, steps a and b. It was reacted with 4-[1-(triphenylmethyl)imidazol-4-yl]butanal (Example 5, step c) according to the procedure of Example 5, step d to produce *tert*-butyl (1-(((cyclohexylmethyl amino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate. This was converted to the title compound using the procedure of Example 1, steps e to g. Thus, the title compound (R_f 0.4, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a colourless oil: ^{1}H NMR (300MHz, *d4*-MeOH) 7.54(1H, d), 6.77(1H, d), 3.01(2H, dd), 2.85(2H, d), 2.60(2H, t), 1.73(9H, m), 1.57(3H, m), 1.23(3H, m), 0.93(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 53.07, H 7.40, N 9.93%; $C_{19}H_{31}N_3O_6S$ requires: C 53.13, H7.27, N 9.78%.

Example 18

N- *Cyclohexylmethyl-2-hydroxy-5-(1H-imidazol-4-yl)-1-pentanesulfonamide*

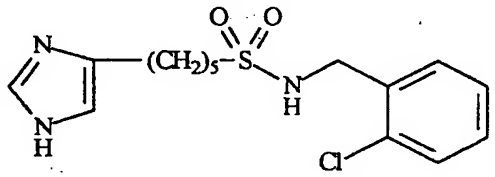


tert-Butyl (1-(((cyclohexylmethylamino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate (Example 17) was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.15, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a colourless oil: ^{1}H NMR (300MHz, *d4*-MeOH) 7.57(1H, d), 6.79(1H, s), 4.09(1H, m), 3.12(2H, d), 2.87(2H, d), 2.62(2H, t), 1.73(10H, m), 1.26(3H, m), 0.93(2H, m). The maleate salt was

prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan.

Example 19

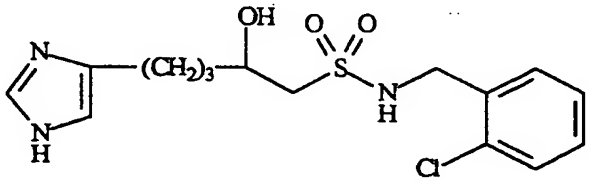
N-(2-Chlorobenzyl)-5-(1H-imidazol-4-yl)-1-pentanesulfonamide



N-(*tert*-Butoxycarbonyl)-*N*-(2-chlorobenzyl)-methanesulfonamide was prepared from (2-chlorobenzyl)amine essentially according to the procedure of Example 1, steps a and b. It was reacted with 4-[1-(triphenylmethyl)imidazol-4-yl]butanal (Example 5, step c) according to the procedure of Example 5, step d to produce *tert*-butyl (1-((((2-chlorobenzyl)amino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate. This was converted to the title compound using essentially the procedure of Example 1, steps e to g, with the modification to step f that the palladium catalyst was replaced by rhodium-on-alumina.. Thus, the title compound (R_f 0.2, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a colourless oil: ^{1}H NMR (300MHz, *d4*-MeOH) 7.56(1H, s), 7.50(1H, m), 7.39(1H, m), 7.31(2H, m), 6.75(1H, s), 4.22(2H, s), 2.89(2H, dt), 2.56(2H, dt), 1.72(2H, m), 1.59(2H, m), 1.37(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 49.59, H 5.30, N 8.95%; $C_{19}H_{24}ClN_3O_6S$ requires: C 49.83, H 5.28, N 9.18%.

Example 20

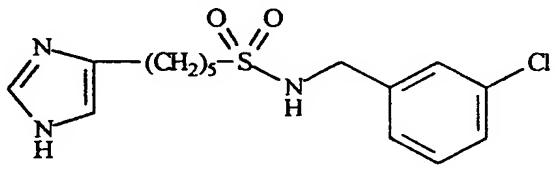
N-(2-Chlorobenzyl)-2-hydroxy-5-(1H-imidazol-4-yl)-1-pentanesulfonamide



tert-Butyl (1-((((2-chlorobenzyl)amino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate (Example 19) was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.2, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a colourless oil: ^{1}H NMR (300MHz, *d*$_4$-MeOH) 7.57(1H, s), 7.53(1H, m), 7.39(1H, m), 7.30(2H, m), 6.78(1H, s), 4.37(2H, s), 4.09(1H, m), 3.08(2H, m), 2.60(2H, t), 1.71(2H, m), 1.54(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 49.59, H 5.30, N 8.95%; $C_{19}H_{24}ClN_3O_6S$ requires: C 49.83, H 5.28, N 9.18%.

Example 21

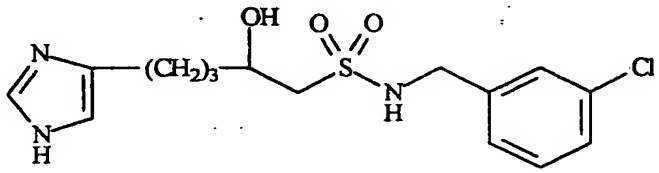
N-(3-Chlorobenzyl)-5-(1H-imidazol-4-yl)-1-pentanesulfonamide



N-(*tert*-Butoxycarbonyl)-*N*-(3-chlorobenzyl)-methanesulfonamide was prepared from (3-chlorobenzyl)amine essentially according to the procedure of Example 1, steps a and b. It was reacted with 4-[1-(triphenylmethyl)imidazol-4-yl]butanal (Example 5, step c) according to the procedure of Example 5, step d to produce *tert*-butyl (1-((((3-chlorobenzyl)amino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate. This was converted to the title compound using the procedure of Example 1, steps e, f and g, with the modification to step f that the palladium catalyst was replaced by rhodium-on-alumina. Thus, the title compound (R_f 0.3, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a colourless oil: ^{1}H NMR (300MHz, *d*$_4$-MeOH) 7.56(1H, s), 7.50(1H, m), 7.39(1H, m), 7.31(2H, m), 6.75(1H, s), 4.22(2H, s), 2.89(2H, dt), 2.56(2H, dt), 1.72(2H, m), 1.59(2H, m), 1.37(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 49.84, H 5.26, N 9.08%; $C_{19}H_{24}ClN_3O_6S$ requires: C 49.83, H 5.28, N 9.18%.

Example 22

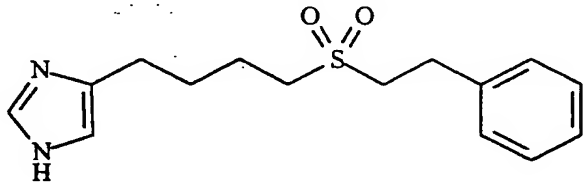
N-(3-Chlorobenzyl)-2-hydroxy-5-(1H-imidazol-4-yl)-1-pentanesulfonamide



tert-Butyl (1-((((3-chlorobenzyl)amino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate (Example 21) was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.2, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a colourless oil: ^{1}H NMR (300MHz, *d4*-MeOH) 7.56(1H, s), 7.41(1H, s), 7.28(3H, m), 6.78(1H, s), 4.23(2H, s), 4.08(1H, m), 3.11(2H, m), 2.61(2H, t), 1.71(2H, m), 1.56(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan.

Example 23

[4-(1H-Imidazol-4-yl)butyl] phenethyl sulfone



Step a. *2-(*tert*-butyldimethylsilyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole.* A solution of 1-(*N,N*-dimethylsulfamoyl)-imidazole[3] (4.48g, 25.6mmol) in tetrahydrofuran (100ml) was cooled under an atmosphere of argon to –78°C. *n*-Butyl lithium (1.5M in hexanes) (18.0ml, 27.0mmol) was added over 30min and the solution stirred for a further 30min. To the resulting brown solution was added over 15min a solution of *tert*-butyldimethylsilyl chloride (4.37g, 28.2mmol) in tetrahydrofuran (20ml). The solution was allowed to warm to room temperature and stirred for 24h. Saturated ammonium chloride solution (100ml) and diethyl ether (100ml) were added and the ethereal extract was washed with brine and dried over magnesium sulfate. Filtration and evaporation of

the filtrate gave an oily residue, which was purified by flash column chromatography (silica; ethyl acetate) to afford the product as an amber solid (6.97g).

Step b. *5-(4- bromobutyl)-2-(*tert-*butyldimethylsilyl)-1-(*N,N-*dimethylsulfamoyl)-imidazole.* A solution of the product from step a (4.00g, 14.5mmol) in tetrahydrofuran (45ml) was cooled under an atmosphere of argon to -78°C. *n*-Butyl lithium (1.5M in hexanes) (10.15ml, 15.2mmol) was added over 15min and the solution stirred for a further 30min. A solution of 1,4-dibromobutane (1.96ml, 16.4mmol) in tetrahydrofuran (5ml) was added over 10min. The solution was stirred for 30min, allowed to warm to room temperature and stirred for 18h. Saturated ammonium chloride solution (50ml) and diethyl ether (50ml) were added and the organic extract was washed with water and dried over magnesium sulfate. Filtration, evaporation of the filtrate and purification by flash column chromatography (silica; 20% ethyl acetate/hexane) afforded the product (R_f 0.23) as a pale yellow crystalline solid (1.87g): ^{1}H NMR (300MHZ, $CDCl_3$) 6.97 (1H, s), 3.46 (2H, t), 2.84 (6H, s), 2.76 (2H, t), 2.00–1.78 (4H, m), 1.01 (9H, s), 0.39 (6H, s).

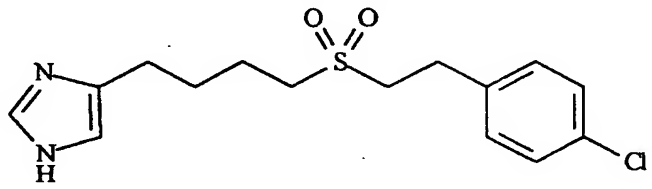
Step c. *4-[2-(*tert-*butyldimethylsilyl)-1-(*N,N-*dimethylsulfamoyl)imidazol-5-yl]butyl phenethyl sulfide.* To a suspension of the product from step b (701mg, 1.71mmol) and potassium carbonate (283mg, 2.05mmol) in *N,N*-dimethylformamide (3ml) was added phenethyl mercaptan (229µl, 1.71mmol). The reaction was stirred at room temperature for 6h before the addition of brine (10ml). The product was extracted with ethyl acetate (2x20ml) and the combined organic material washed with water (3x20ml) before drying over magnesium sulfate. Filtration and evaporation of the filtrate furnished the title compound as a pale yellow oil in quantitative yield: ^{1}H NMR (300MHZ, $CDCl_3$) 7.33-7.20 (5H, m), 6.95 (1H, s), 2.98–2.70 (6H, m), 2.78 (6H, s), 2.58 (2H, t), 1.76-1.73 (4H, m), 1.01 (9H, s), 0.39 (6H, s).

Step d. A solution of the product from step c (883mg, 1.89mmol) in methanol (8ml) at 0°C was treated with a slurry of Oxone® (3.48g, 5.66mmol) in water (8ml) portionwise and the resulting suspension stirred for 4.5h at room temperature. The reaction was diluted with water, the product extracted with chloroform (3x30ml) and the combined

organic extracts washed with water and brine before drying over sodium sulfate. Filtration and evaporation of the filtrate gave a colourless oil which was heated at reflux in an ethanol (15ml)/ 2M hydrochloric acid (8ml) solution for 24h. Solvent evaporation, treatment of the residue with methanolic ammonia and re-evaporation afforded a residue suitable for purification by flash column chromatography (silica; 1:10:90 ammonia(880)/methanol/dichloromethane). Thus, the title compound (R_f 0.27) was isolated as a colourless oil (433mg): ^{1}H NMR (300MHZ, *d4*-MeOH) 7.56 (1H, d), 7.34–7.23 (5H, m), 6.80 (1H, d), 3.37–3.32 (2H, m), 3.12-3.02 (4H, m), 2.61 (2H, t), 1.80–1.74 (4H, m). Found: C 61.41, H 6.97, N 9.36%; $C_{15}H_{20}N_2O_2S$ requires: C 61.62, H 6.89, N 9.58%.

Example 24

[4-(1H-Imidazol-4-yl)butyl] 4-chlorophenethyl sulfone



Step a. *1-chloro-2-(4-chlorophenyl)ethane.* To a solution of 4-chlorophenethyl alcohol (5ml, 37mmol) and pyridine (3.0ml, 37.0mmol) in a two-necked flask, equipped with a dropping funnel and a reflux condenser fitted with calcium chloride drying tube, was added thionyl chloride (5.39ml, 74.0mmol) dropwise over 1h. The reaction was heated at reflux for 1.5h before being cooled in an ice-bath. This led to the precipitation of a white solid which was filtered off rapidly and washed with a small quantity of cold diethyl ether. The organic material was then washed cautiously with water (1x30ml), 2N sodium hydroxide solution (2x30ml) and water (1x30ml), dried over magnesium sulfate, filtered and the solvent evaporated to give the desired product as a pale yellow oil (5.73g): ^{1}H NMR (300MHZ, $CDCl_3$) 7.29 (2H, d), 7.16 (2H, d), 3.70 (2H, t), 3.05 (2H, t).

Step b. S-*(4-chlorophenethyl)isothiouronium chloride.* A solution of the product from step a (4.98g, 28.4mmol) and thiourea (2.16g, 28.4mmol) in ethanol (35ml) was heated at reflux for 22h. Solvent evaporation and trituration of the resultant residue with

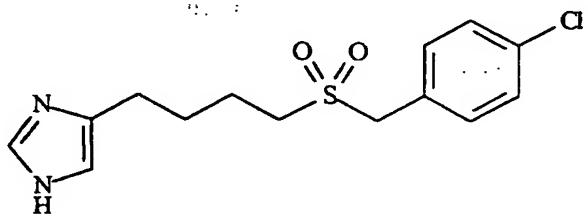
diethyl ether afforded a solid which was isolated by filtration, washed with diethyl ether and dried in vacuo at 50°C to furnish the product as a pale brown solid (5.42g).

Step c. *4-chlorophenethyl thiol.* The product from step b (500mg, 2.0mmol) was heated at reflux in a solution of sodium hydroxide (120mg, 3.0mmol) in water (2.5ml) for 2h. The reaction mixture was allowed to cool before acidification using dilute sulfuric acid and product extraction using diethyl ether (10ml). The organic material was washed with water (2x20ml), dried over sodium sulfate, filtered and the solvent evaporated to give the desired compound as a pale yellow oil (227mg): ^{1}H NMR (300MHZ, $CDCl_3$) 7.31-7.26 (2H, m), 7.15–7.10 (2H, m), 2.94–2.88 (2H, m), 2.81–2.73 (2H, m), 1.37 (1H, t).

Step d. 5-(4-Bromobutyl)-2-(*tert*-butyldimethylsilyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole (410mg, 1.00mmol) (Example 23, step b) was reacted with the product from step c (227mg, 1.32mmol) in essentially the same manner as the synthesis of Example 23, steps c and d to yield, after purification by flash column chromatography (R_f 0.35, silica; 1:10:90 ammonia(880)/methanol/dichloromethane), the title compound as a white crystalline solid (41mg): ^{1}H NMR (300MHZ, d_4-MeOH) 7.57 (1H, dd), 7.32–7.25 (4H, m), 6.81 (1H, s), 3.34 (2H, m), 3.10–3.03 (4H, m), 2.62 (2H, m), 1.84–1.73 (4H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan.

Example 25

[4-(1H-Imidazol-4-yl)butyl]-4-chlorobenzyl sulfone



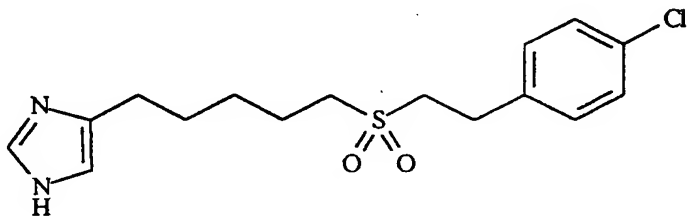
Step a. *4-[2-(tert-butyldimethylsilyl)-1-(N,N-dimethylsulfamoyl)imidazol-5-yl]butyl 4-chlorobenzyl sulfide.* 5-(4-Bromobutyl)-2-(*tert*-butyldimethylsilyl)-1-(*N,N*-dimethylsulfamoyl) imidazole (484mg, 1.18mmol) (Example 23, step b) and 4-chlorobenzyl mercaptan (156µl, 1.18mmol) were reacted together in a manner

analogous to Example 23, step c to afford the desired compound as a pale yellow oil in quantative yield: ^{1}H NMR (300MHZ, $CDCl_3$) 7.26 (4H, m), 6.93 (1H, s), 3.67 (2H, s), 2.81 (6H, s), 2.69 (2H, t), 2.44 (2H, t), 1.70 (4H, m), 1.00 (9H, s), 0.39 (6H, s).

Step b. A solution of the product from step a (599mg, 1.23mmol) was further reacted according to Example 23, step d to yield the title compound as a white crystalline solid (265mg): ^{1}H NMR (300MHZ, *d4*-MeOH) 7.57 (1H, dd), 7.41 (4H, s), 6.79 (1H, s), 4.37 (2H, s), 3.00 (2H, dd), 2.62 (2H, t), 1.79–1.77 (4H, m).

Example 26

[5-(1H-Imidazol-4-yl)pentyl] 4-chlorophenethyl sulfone



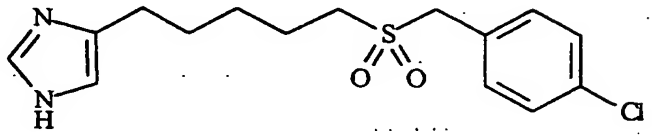
Step a. *5-(5-bromopentyl)-2-(*tert*-butyldimethylsilyl)-1-(*N,N*-dimethylsulfamoyl) imidazole.* The synthesis of this compound was achieved in an analogous fashion to that of Example 23, step b, employing 1,5-dibromopentane as the electrophilic reagent: ^{1}H NMR (300MHZ, $CDCl_3$) 6.95 (1H, s), 3.43 (2H, t), 2.84 (6H, s), 2.73 (2H, t), 1.95–1.90 (2H, m), 1.72–1.70 (2H, m), 1.59–1.57 (2H, m), 1.01 (9H, s), 0.39 (6H, s).

Step b. The product from step a (444mg, 1.05mmol) was reacted with 4-chlorophenethyl thiol (190mg, 1.1mmol) (Example 24, step c) according to the procedure for Example 23, step c. Subsequent oxidation and deprotection of the adduct was performed according to Example 23, step d to afford, after purification by flash column chromatography (R_f 0.3, silica; 1:10:90 ammonia (880)/methanol/dichloromethane), the title compound as a white crystalline solid (25mg): ^{1}H NMR (300MHZ, *d4*-MeOH) 7.54 (1H, d), 7.33–7.26 (4H, m), 6.77 (1H, s), 3.37–3.30 (2H, m), 3.11–2.99 (4H, m), 2.59 (2H, t), 1.80 (2H, quin.), 1.66 (2H, quin.), 1.45 (2H, quin.). The maleate salt was prepared by lyophilisation of an equimolar

solution of the product and maleic acid in water/dioxan. Found: C 52.62, H 5.66, N 6.24%; $C_{20}H_{25}ClN_2O_6S$ requires: C 52.57, H 5.51, N 6.13%.

Example 27

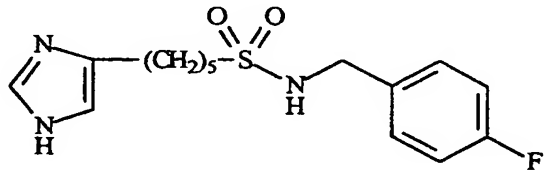
[5-(1H-Imidazol-4-yl)pentyl] 4-chlorobenzyl sulfone



5-(5-Bromopentyl)-2-(*tert*-butyldimethylsilyl)-1-(*N,N*-dimethylsulfamoyl) imidazole (Example 26, step a) (385mg, 0.91mmol) was reacted with 4-chlorobenzyl mercaptan (126µl, 0.95mmol) in a manner analogous to Example 23, step c. The crude product was subjected to oxidation and deprotection according to the procedure for Example 23, step d. Purification of the adduct was achieved *via* preparative reverse phase hplc (R_t 9.63 min; C_{18} ; 40% acetonitrile/60% water + 0.1% triethylamine) to give the title compound as a colourless oil (20mg). ^{1}H NMR (300MHZ, *d4*-MeOH) 7.60 (1H, s), 7.40 (4H, m), 6.79 (1H, s), 4.38 (2H, s), 3.01 (2H, m), 2.59 (2H, t), 1.80 (2H, quin.), 1.66 (2H, quin.), 1.46 (2H, quin.). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 51.45, H 5.19, N 6.26%; $C_{19}H_{23}ClN_2O_6S$ requires: C 51.52, H 5.23, N 6.32%.

Example 28

N-(4-Fluorobenzyl)-5-(1H-imidazol-4-yl)-1-pentanesulfonamide

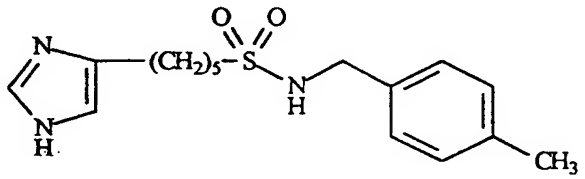


N-(*tert*-Butoxycarbonyl)-*N*-(4-fluorobenzyl)-methanesulfonamide was prepared from (4-fluorobenzyl)amine essentially according to the procedure of Example 1, steps a and b. It was reacted with 4-[1-(triphenylmethyl)imidazol-4-yl]butanal (Example 5, step c) according to the procedure of Example 5, step d to produce *tert*-butyl (1-((((4-fluorobenzyl)amino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl)

carbonate. This was converted to the title compound using essentially the procedure of Example 1, steps e to g. Thus, the title compound was isolated as a colourless oil: ^{1}H NMR (300MHz, $CDCl_3$) 7.52(1H, s), 7.33(2H, m), 7.04(2H, m), 6.76(1H, s), 4.27(2H, s), 2.93(2H, t), 2.61(2H, t), 1.80(2H, quin.), 1.65(2H, quin.), 1.45(2H, quin.). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 51.50, H 5.60, N 9.41%; $C_{19}H_{24}FN_3O_6S$ requires: C 51.69, H 5.48, N 9.52%.

Example 29

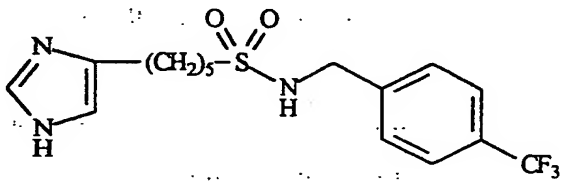
N-(4-Methylbenzyl)-5-(1H-imidazol-4-yl)-1-pentanesulfonamide



N-(*tert*-Butoxycarbonyl)-*N*-(4-methylbenzyl)-methanesulfonamide was prepared from (4-methylbenzyl)amine essentially according to the procedure of Example 1, steps a and b. It was reacted with 4-[1-(triphenylmethyl)imidazol-4-yl]butanal (Example 5, step c) according to the procedure of Example 5, step d to produce *tert*-butyl (1-((((4-methylbenzyl benzyl)amino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate. This was converted to the title compound using essentially the procedure of Example 1, steps e to g. Thus, the title compound was isolated as a colourless oil: ^{1}H NMR (300MHz, *d6*-DMSO) 11.70(1H, br s), 7.52(1H, t), 7.47(1H, s), 7.20(2H, d), 7.12(2H, d), 6.68(1H, s), 4.06(2H, d), 2.83(2H, t), 2.43(2H, t), 1.60(2H, m), 1.49(2H, m), 1.27(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 51.73, H 6.44, N 9.17%; $C_{19}H_{27}N_3O_6S.1.4H_2O$ requires: C 51.83, H 6.50, N 9.07%.

Example 30

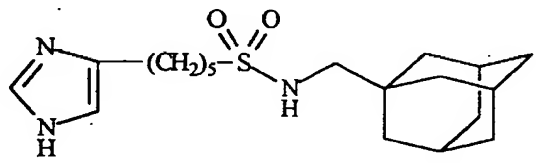
N-(4-Trifluoromethylbenzyl)-5-(1H-imidazol-4-yl)-1-pentanesulfonamide



N-(*tert*-Butoxycarbonyl)-*N*-(4-trifluoromethylbenzyl)-methanesulfonamide was prepared from (4-trifluoromethylbenzyl)amine essentially according to the procedure of Example 1, steps a and b. It was reacted with 4-[1-(triphenylmethyl)imidazol-4-yl]butanal (Example 5, step c) according to the procedure of Example 5, step d to produce *tert*-butyl (1-((((4-trifluoromethylbenzyl)amino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate. This was converted to the title compound using essentially the procedure of Example 1, steps e to g. Thus, the title compound was isolated as a colourless oil: ^{1}H NMR (300MHz, *d*$_6$-DMSO) 7.71(2H, d), 7.56(2H, d), 7.51(1H, s), 6.71(1H, s), 4.23(2H, s), 2.95(2H, t), 2.45(2H, t), 1.63(2H, m), 1.53(2H, m), 1.34(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 44.07, H 5.29, N 7.61%; $C_{20}H_{24}F_3N_3O_6S.2.8H_2O$ requires: C 44.30, H 5.51, N 7.75%.

Example 31

N-(1-Adamantylmethyl)-5-(1H-imidazol-4-yl)-1-pentanesulfonamide

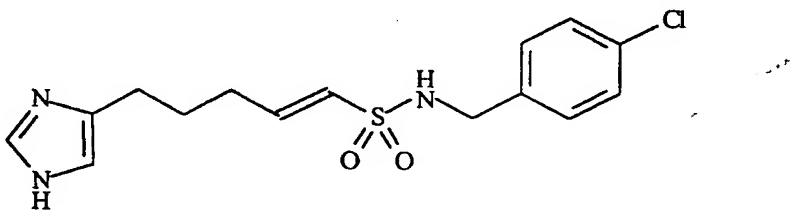


N-(*tert*-Butoxycarbonyl)-*N*-(1-adamantylmethyl)-methanesulfonamide was prepared from 1-adamantylmethylamine essentially according to the procedure of Example 1, steps a and b. It was reacted with 4-[1-(triphenylmethyl)imidazol-4-yl]butanal (Example 5, step c) according to the procedure of Example 5, step d to produce *tert*-butyl (1-adamantylmethyl)amino)sulfonyl)methyl)-4-(1-(triphenylmethyl)imidazol-4-yl)butyl) carbonate. This was converted to the title compound using essentially the procedure of Example 1, steps e to g. Thus, the title compound was isolated as a

colourless oil: ^{1}H NMR (300MHz, *d4*-MeOH) 7.56(1H, d), 6.77(1H, s), 3.01(2H, m), 2.67(2H, m), 2.60(2H, m), 1.97(3H, br s), 1.72(10H, m), 1.50(8H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 57.07, H 7.47, N 8.51%; $C_{23}H_{35}N_3O_6S$ requires: C 57.36, H 7.35, N 8.73%.

Example 32

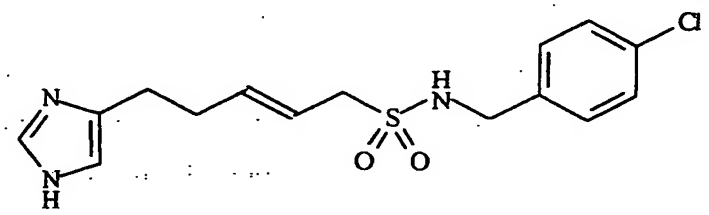
(E)-N-(4-Chlorobenzyl)-5-(1H-imidazol-4-yl)-1-pent-1-enesulfonamide



(E)-N-(4-Chlorobenzyl)-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pent-1-enesulfonamide (Example 5, step e) (100mg, 0.17mmol) was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.30, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a colourless oil (47mg, 80%): ^{1}H NMR (300MHz, $CDCl_3$) 7.54(1H, s), 7.28(4H, m), 6.76(1H, s), 6.70(1H, m), 6.12(1H, d, J=15Hz), 4.15(2H, s), 2.61(2H, m), 2.23(2H, m), 1.78(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 51.55, H 5.32, N 9.26%; $C_{19}H_{22}ClN_3O_6S$ requires: C 51.55, H 4.86, N 9.22%.

Example 33

(E)-N-(4-Chlorobenzyl)-5-(1H-imidazol-4-yl)-1-pent-2-enesulfonamide

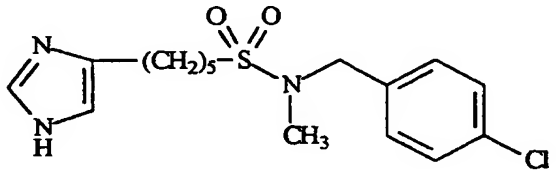


Step a. *(E)-N-(4-chlorobenzyl)-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pent-2-enesulfonamide*. A solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-chlorobenzyl)-methanesulfonamide (Example 1, step b) (640mg, 2.00mmol) in THF (10ml) was cooled to −78°C, 1M potassium *t*-butoxide (4.00ml, 4.00mmol) was added dropwise and the solution was stirred for 1h. A solution of *4-[1-(triphenylmethyl)imidazol-4-yl]butanal* (Example 5, step c) (760mg, 2.00mmol) in THF (10ml) was added by means of a cannula. The mixture was stirred overnight, allowing it to warm slowly to room temperature. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate, filtered and the solvent evaporated. Flash column chromatography (silica, 20% ethyl acetate/dichloromethane) of the residue gave the product as a colourless oil (161mg, 12%).

Step b. The product from the previous step was deprotected and purified according to the procedure of Example 1, step g and the title compound (R_f 0.40, 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a colourless oil: ^{1}H NMR (300MHz, $CDCl_3$) 7.31(4H, m), 7.22(1H, s), 6.70(1H, s), 5.61(1H, dt, J=14.4, 7.2Hz), 5.30(1H, dt, J=14.4, 7.5Hz), 4.26(2H, s), 3.54(2H, d, J=7.5Hz), 2.65(2H, m), 2.32(2H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 48.88, H 5.78, N 8.27%; $C_{19}H_{22}ClN_3O_6S.1.0H_2O$ requires: C 49.02, H 5.76, N 8.57%.

Example 34

N-(4-Chlorobenzyl)-N-methyl-5-(1H-imidazol-4-yl)-1-pentanesulfonamide



Step a. *(E)-N-(4-chlorobenzyl)-N-methyl -5-(1-(triphenylmethyl)imidazol-4-yl)-1-pent-1-enesulfonamide.* A suspension of *(E)-N*-(4-chlorobenzyl)-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pent-1-enesulfonamide (Example 5, step e) (297mg, 0.51mmol) in dry dimethylformamide (1.7ml) was cooled in ice. Sodium hydride (60% dispersion in oil) (22mg, 0.56mmol) was added, the cold bath was removed and the mixture was stirred for 1h, giving a solution. Iodomethane (48µl. 0.77mmol) was added and stirring was continued overnight. The reaction was quenched with water (10ml) and extracted with DCM (3x5ml). The combined extracts were evaporated and the residue taken up in ethyl acetate (10ml). The solution was washed four times with brine, dried over sodium sulfate, filtered and the solvent evaporated. Flash column chromatography (silica, 50% ethyl acetate/toluene) of the residue gave the product as a yellow oil (174mg, 57%).

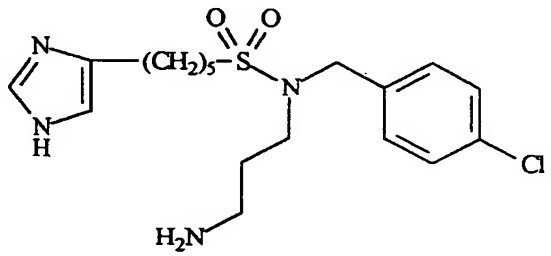
Step b. *N-(4-chlorobenzyl)-N-methyl-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pentanesulfonamide.* A round bottom flask containing the product from the previous step (174mg, 0.29mmol), 10% palladium-on-charcoal (18mg) and THF (17ml) was evacuated and flushed with hydrogen three times. The mixture was vigorously stirred overnight under an atmosphere of hydrogen. The catalyst was removed by filtration and the filtrate evaporated to give the product as a colourless oil (155mg, 89%).

Step c. Trifluoroacetic acid (2ml) was added to the product from the previous step (155mg, 0.26mmol). The flask was stoppered and the resultant yellow solution left to stand overnight under ambient conditions. The solvent was evaporated and the residue purified by flash column chromatography (silica; 1:10:90 ammonia(880)/methanol/dichloromethane). Thus, the title compound (R_f 0.35) was isolated as a colourless oil (83mg, 90%): ^{1}H NMR (300MHz, *d4*-MeOH) 7.56(1H, s), 7.35(4H, s), 6.78(1H, s), 4.30(2H, s), 3.08(2H, m), 2.73(3H, s), 2.60(2H, t), 1.81(2H,

quin.), 1.68(2H, quin.), 1.49(2H, quin.). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 51.08, H 5.60, N 8.92%; $C_{20}H_{26}ClN_3O_6S$ requires: C 50.90, H 5.55, N 8.90%.

Example 35

N-(4-Chlorobenzyl)-N-(3-aminopropyl)-5-(1H-imidazol-4-yl)-1-pentanesulfonamide



Step a. *(E)-N-(4-chlorobenzyl)-N-(3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl)-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pent-1-enesulfonamide.* A solution of *(E)-N-*(4-chlorobenzyl)-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pent-1-enesulfonamide (Example 5, step e) (212mg, 0.36mmol) in dry dimethylformamide (2ml) was cooled in ice. Sodium hydride (60% dispersion in oil) (16mg, 0.40mmol) was added, the cold bath was removed and the mixture was stirred for 30min, giving a solution. *N-*(3-bromopropyl)phthalimide (48µl. 0.77mmol) was added and the solution was heated at 80°C overnight. The reaction was quenched with water (10ml) and extracted with DCM (3x5ml). The combined extracts were evaporated and the residue taken up in ethyl acetate (10ml). The solution was washed four times with brine, dried over sodium sulfate, filtered and the solvent evaporated. Flash column chromatography (silica, 50% ethyl acetate/toluene) of the residue gave the product as a colourless oil (147mg, 53%).

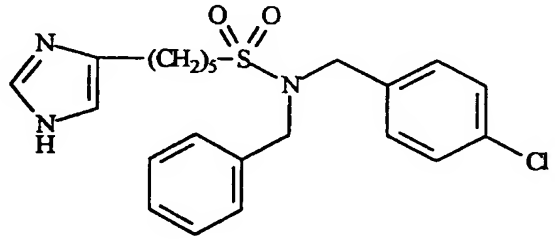
Step b. *N-(4-chlorobenzyl)-N-(3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl)-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pentanesulfonamide.* A round bottom flask containing the product from the previous step (147mg, 0.19mmol), 10% palladium-on-charcoal (12mg) and THF (15ml) was evacuated and flushed with hydrogen three times. The mixture was vigorously stirred overnight under an atmosphere of hydrogen. The catalyst was removed by filtration and the filtrate evaporated to give the product as a colourless oil (57mg, 39%).

Step c. N-*(4-chlorobenzyl)*-N-*(3-aminopropyl)-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pentanesulfonamide*. A solution of the product from the previous step (57mg, 0.071mmol) and hydrazine hydrate (20µl, 0.36mmol) in ethanol (1ml) was heated at reflux for 2h. The precipitate was removed by filtration and the filtrate evaporated. The residue was extraced by trituration with chloroform. The extract was evaporated to give the product as a colourless oil in quantitative yield.

Step d. Trifluoroacetic acid (0.5ml) was added to the product from the previous step. The flask was stoppered and the resultant yellow solution left to stand overnight under ambient conditions. The solvent was evaporated and the residue purified by flash column chromatography (silica; 2:20:80 ammonia(880)/methanol/dichloromethane). Thus, the title compound (R_f 0.50) was isolated as a colourless oil (11mg, 43%): ^{1}H NMR (300MHz, *d4*-MeOH) 7.55(1H, s), 7.41(2H, d), 7.36(2H, d), 6.77(1H, s), 4.39(2H, s), 3.28(2H, t), 3.06(2H, m), 2.59(4H, dd), 1.80(2H, m), 1.70(2H, m), 1.57(2H, m), 1.47(2H, m).

Example 36

N-*Benzyl*-N-*(4-chlorobenzyl)-5-(1*H-*imidazol-4-yl)-1-pentanesulfonamide*



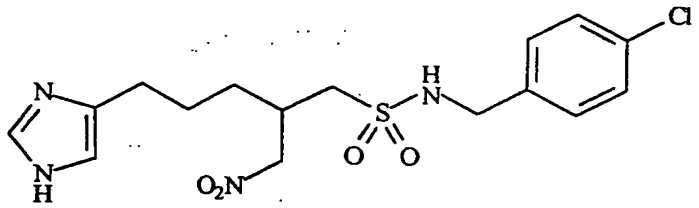
Step a. N-*benzyl*-N-*(4-chlorobenzyl)-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pentanesulfonamide*. A solution of *N*-benzyl-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pentanesulfonamide (see Example 13) (155mg, 0.28mmol) in THF (2ml) was cooled to -78°C and 1.5M lithium diisopropylamide (380µl, 0.56mmol) was added dropwise. The solution was stirred at 0°C for 1h and a solution of 4-chlorobenzyl bromide (58mg, 0.28mmol) in THF (1ml) was added by means of a cannula. The cold bath was removed and the mixture was stirred overnight. The reaction was quenched by the

addition of saturated ammonium chloride solution (10ml) and the mixture was extracted with ethyl acetate (10ml). The organic phase was washed with water and brine and dried over sodium sulfate. Flash column chromatography (silica, ethyl acetate) gave the product as a colourless oil (100mg, 53%).

Step b. Trifluoroacetic acid (2ml) was added to the product from the previous step (100mg, 0.15mmol). The flask was stoppered and the resultant yellow solution left to stand overnight under ambient conditions. The solvent was evaporated and the residue purified by flash column chromatography (silica; 1:10:90 ammonia(880)/methanol/dichloromethane). Thus, the title compound (R_f 0.40) was isolated as a colourless oil (41mg, 64%): ^{1}H NMR (300MHz, *d4*-MeOH) 7.56(1H, s), 7.25(9H, m), 6.77(1H, s), 4.35(4H, s), 3.01(2H, m), 2.58(2H, t), 1.77(2H, quin.), 1.63(2H, quin.), 1.42(2H, quin.). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 56.69, H 5.65, N 7.85%; $C_{26}H_{30}ClN_3O_6S$ requires: C 56.98, H 5.52, N 7.67%.

Example 37

N-(4-Chlorobenzyl)-2-nitromethyl-5-(1H-imidazol-4-yl)-1-pentanesulfonamide

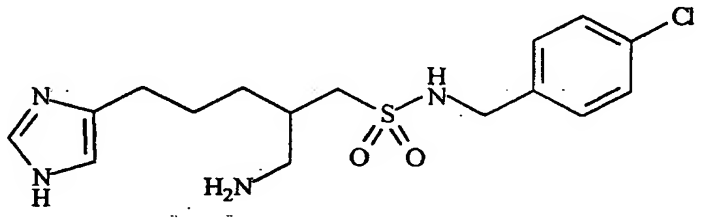


Step a. *N-(4-chlorobenzyl)-2-nitromethyl-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pentanesulfonamide.* To a mixture of *(E)-N*-(4-chlorobenzyl)-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pent-1-enesulfonamide (Example 5, step e) (291mg, 0.50mmol), nitromethane (5ml) and THF (5ml) was added [2.2.2]-diazabicylcoundecene (224µl, 1.50mmol). The solution was heated at reflux for 2h, allowed to cool and the solvent evaporated. The residue was purified by flash column chromatography (silica, 5% methanol/DCM) to give the product as a white solid (281mg, 87%).

Step b. Trifluoroacetic acid (2ml) was added to the product from the previous step (150mg, 0.23mmol). The flask was stoppered and the resultant yellow solution left to stand overnight under ambient conditions. The solvent was evaporated and the residue purified by flash column chromatography (silica; 1:10:90 ammonia(880)/methanol/dichloromethane). Thus, the title compound (R_f 0.40) was isolated as a colourless oil (82mg, 87%): ^{1}H NMR (300MHz, $CDCl_3$) 7.42(1H, s), 7.32(4H, m), 6.75(1H, s), 4.55(2H, ddd), 4.28(2H, s), 3.16(1H, dd), 3.00(1H, dd), 2.73(1H, m), 2.60(2H,t), 1.65(3H, m), 1.47(1H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 46.28, H 4.93, N 10.57%; $C_{20}H_{25}ClN_4O_8S$ requires: C 46.47, H 4.88, N 10.84%.

Example 38

2-Aminomethyl -N-*(4-chlorobenzyl)-5-(1*H*-imidazol-4-yl)-1-pentanesulfonamide*



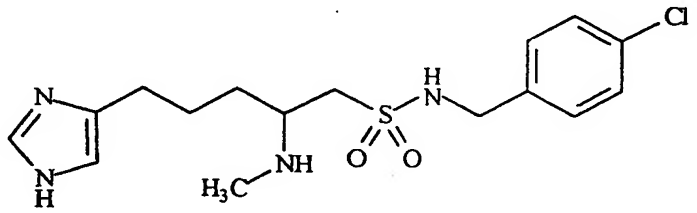
Step a. *2-aminomethyl*-N-*(4-chlorobenzyl)-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pentanesulfonamide.* A round bottom flask containing *N*-(4-chlorobenzyl)-2-nitromethyl-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pentanesulfonamide (Example 37, step a) (260mg, 0.41mmol), Raney nickel (20mg) and THF (10ml) was evacuated and flushed with hydrogen three times. The mixture was vigorously stirred overnight under an atmosphere of hydrogen. The catalyst was removed by filtration through Celite and the residue washed with 50% methanol/DCM. The filtrate was evaporated and the residue purified by flash column chromatography (silica, 1:10:90 ammonia(880)/methanol/dichloromethane) to give the product as a white solid (155mg, 62%).

Step b. A mixture of the product from the previous step (155mg, 0.25mmol), ethanol (5ml) and 2M hydrochloric acid (1ml) was heated at reflux for 1.5h. The solvent was

evaporated and residual hydrochloric acid was removed by co-evaporation with ethanol (2x10ml). The residue was taken up in a little ethanol and the product was precipitated by the addition of diethyl ether. The precipitate was collected by filtration and dried in vacuo over phosphorus pentoxide. Thus the dihydrochloride salt of the title compound was obtained as a white solid (80mg, 72%): ^{1}H NMR (300MHz, *d6*-DMSO) 9.00(1H, s), 8.21(3H, br s), 7.88(1H, t), 7.39(5H, m), 4.18(2H, m), 3.36(1H, m), 3.01(2H, m), 2.85 (1H, m), 2.63(2H, t), 2.15(1H, m), 1.70(2H, m), 1.42(2H, m). Found: C 40.09, H 5.93, N 11.42%; $C_{16}H_{25}Cl_3N_4O_2S.2.0H_2O$ requires: C 40.05, H 6.09, N 11.68%.

Example 39

N-(4-Chlorobenzyl)-2-methylamino-5-(1H-imidazol-4-yl)-1-pentanesulfonamide



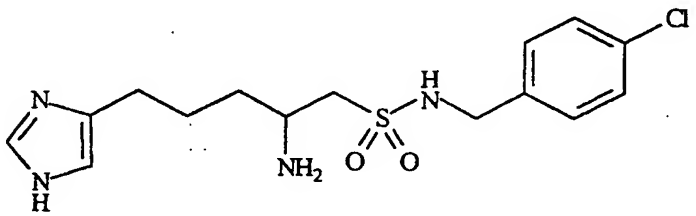
Step a. *N-(4-chlorobenzyl)-2-methylamino-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pentanesulfonamide*. A mixture of *(E)-N*-(4-chlorobenzyl)-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pent-1-enesulfonamide (Example 5, step e) (291mg, 0.50mmol), 33% methylamine in industrial methylated spirit (5ml) and THF (5ml) was sealed in a Teflon-lined pressure vessel and heated at 80°C for 5h. The solution was allowed to cool and the solvent evaporated. The residue was purified by flash column chromatography (silica, 5% methanol/DCM then 1:10:90 ammonia(880)/methanol/dichloromethane) to give the product as a white solid (213mg, 69%).

Step b. A mixture of the product from the previous step (213mg, 0.35mmol), ethanol (5ml) and 2M hydrochloric acid (1ml) was heated at reflux for 2h. The solvent was evaporated and residual hydrochloric acid was removed by co-evaporation with ethanol (2x10ml). The residue was taken up in a little ethanol and the product was precipitated by the addition of diethyl ether. The precipitate was collected by filtration and dried in vacuo over phosphorus pentoxide. Thus the dihydrochloride salt of the title compound

was obtained as a white solid (123mg, 79%): ^{1}H NMR (300MHz, *d*$_6$-DMSO) 9.00(1H, d), 8.18(1H, t), 7.39(5H, m), 4.21(2H, m), 3.62(1H, m), 3.45(2H, m), 2.67(2H, m), 2.56(3H, s), 1.80(2H, m). Found: C 41.66, H 5.84, N 12.21%; $C_{16}H_{25}Cl_3N_4O_2S.1.0H_2O$ requires: C 41.61, H 5.89, N 12.13%.

Example 40

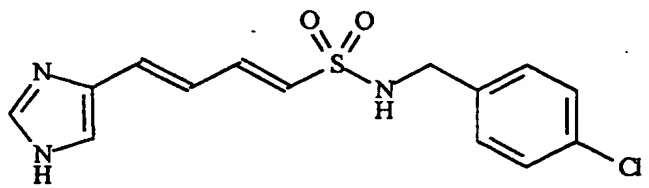
*2-Amino-*N*-(4-chlorobenzyl)-5-(1*H*-imidazol-4-yl)-1-pentanesulfonamide*



A mixture of *(E)-N*-(4-chlorobenzyl)-5-(1-(triphenylmethyl)imidazol-4-yl)-1-pent-1-enesulfonamide (Example 5, step e) (290mg, 0.50mmol), ethanol saturated with ammonia (10ml) and THF (10ml) was sealed in a Teflon-lined pressure vessel and heated at 120°C overnight. The solution was allowed to cool and the solvent evaporated. The residue was purified by flash column chromatography (silica, 1:10:90 ammonia(880)/methanol/dichloromethane) to give the title compound was obtained as a white solid (123mg, 79%): ^{1}H NMR (300MHz, *d*$_6$-DMSO) 7.92(1H, br s), 7.61(1H, d), 7.41(4H, m), 6.58(1H, d), 4.54(1H, m), 4.21(2H, s), 3.65(1H, dd), 3.50(1H, dd), 3.29(2H, s), 2.67(2H, m), 2.65(2H, t), 2.10(1H, m), 1.95(1H, m),1.81(1H, m), 1.66(1H, m). Found: C 50.17, H 5.99, N 15.48%; $C_{15}H_{21}ClN_4O_2S$ requires: C 50.48, H 5.93, N 15.70%.

Example 41

(E,E)-N-*(4-Chlorobenzyl)-4-(1*H*-imidazol-4-yl)-1-but-1,3-dienesulfonamide*



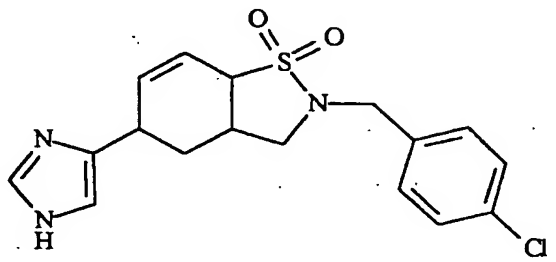
Step a. *3-[1-(triphenylmethyl)imidazol-4-yl]prop-2-en-1-al.* A mixture of manganese dioxide (2.50g, 28.8mmol), 3-[1-(triphenylmethyl)imidazol-4-yl]prop-2-en-1-ol (1.06g, 2.88mmol)[4] and chloroform was heated at reflux for 2.5h. The solid residues were removed by filtration and the filtrate evaporated to afford the product as a white solid (759mg, 72%).

Step b. (E,E)-N-*(4-chlorobenzyl)-4-(1-(triphenylmethyl)imidazol-4-yl)-1-but-1,3-enesulfonamide.* A solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-chlorobenzyl)-methanesulfonamide (Example 1, step b) (658mg, 2.06mmol) in THF (5ml) was cooled to –78°C, 1.5M lithium diisopropylamide (1.37ml, 2.06mmol) was added dropwise and the solution was stirred for 1h. A solution of the product from the previous step (750mg, 2.06mmol) was added by means of a cannula and the solution was stirred overnight, allowing it to warm slowly to room temperature. The reaction mixture was partitioned between saturated ammonium chloride solution (20ml) and ethyl acetate (20ml). The aqueous phase was extracted with ethyl acetate (20ml). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and the solvent evaporated. Flash column chromatography (silica, 10–50% ethyl acetate/DCM) of the residue gave the product as a pale yellow solid (132mg, 11%).

Step c. Trifluoroacetic acid (2ml) was added to the product from the previous step (100mg, 0.15mmol). The flask was stoppered and the resultant yellow solution left to stand overnight under ambient conditions. The solvent was evaporated and the residue purified by flash column chromatography (silica; 1:10:90 ammonia(880)/methanol/dichloromethane). Thus, the title compound (R_f 0.30) was isolated as a colourless oil (54mg, 73%): ^{1}H NMR (300MHz, *d4*-MeOH) 7.74(1H, s), 7.32(4H, m), 7.27(1H, s), 7.11(1H, dd, J=14.7, 10.5Hz), 6.90(1H, d, J=15.6Hz), 6.78(1H, dd, J=15.3, 10.5Hz), 6.34(1H, d, J=14.7Hz), 4.13(2H, s). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 49.09, H 4.16, N 9.60%; $C_{18}H_{18}ClN_3O_6S$ requires: C 49.15, H 4.12, N 9.55%.

Example 42

2-(4-Chlorobenzyl)-5-(1H-imidazol-4-yl)-2,3,3a,4,5,7a-hexahydro-benzo[d]isothiazole 1,1-dioxide



Step a. *methyl 3-[1-(dimethylsulfamoyl)-imidazol-4-yl]propenoate.* To a mixture of methyl 3-[1*H*-imidazol-4-yl]propenoate hydrochloride salt (16.1g, 85.0mmol),[4] triethylamine (37.5ml, 269mmol) and DCM (300ml) was added dimethylsulfamoyl chloride (10ml, 93.1mmol). The solution was heated at reflux overnight, allowed to cool to room temperature, washed with water and brine and dried over magnesium sulfate. Filtration and evaporation afforded a yellow solid, which was recrystallised from isopropanol to give the product as a white solid (17.3g, 78%).

Step b. *3-[1-(dimethylsulfamoyl)-imidazol-4-yl]prop-2-en-1-ol.* A solution of the product from the previous step (1.00g, 3.86mmol) in THF (40ml) was cooled to -15°C (ice/methanol) and lithium aluminium hydride (77mg, 1.93mmol) was added in small portions over 15min. The mixture was stirred at -15°C for 1h. Lithium aluminium hydride (24mg, 0.64mmol) was added in small portions over 10min and mixture was stirred at –15°C for 1h. Without allowing the mixture to warm, the reaction was quenched by the addition of saturated ammonium chloride solution (10ml). The organic phase was decanted and the inorganic residue was washed with diethyl ether (2x40ml). The combined organic phases were washed with brine, dried over sodium sulfate, filtered and evaporated. The residue was purified by flash column chromatography (silica, 2% methanol/ethyl acetate) and the product was isolated as a white solid (220mg, 25%).

Step c. *3-[1-(dimethylsulfamoyl)-imidazol-4-yl]propenal.* A solution of oxalyl chloride (181µl, 2.08mmol) in DCM (6ml) was cooled to –78°C and dimethylsulfoxide (295µl, 4.16mmol) was added dropwise with concomitant effervescence. The solution was

stirred for 10min, by which time effervescence had ceased, and a solution of the product from the previous step (400mg, 1.73mmol) and dimethylsulfoxide (300µl) in DCM (6ml) was added by means of a cannula. The solution was stirred for 20min, triethylamine (671µl, 6.24mmol) was added, the cold bath was removed and the resultant solution stirred for 1h. A column of silica was pre-eluted with an equal volume of ethyl acetate until complete removal of solvent. The reaction mixture was applied to the top of the column and the column eluted to dryness. This was repeated with a column's volume of DCM to ensure complete removal of dimethylsulfide. The column was eluted with ethyl acetate and the aldehyde collected in fractions. Combination of the fractions and evaporation of the solvent gave the product as a white solid (368mg, 93%).

Step d. (E,E)-N-*(4-chlorobenzyl)-4-(1-(dimethylsulfamoyl)-imidazol-4-yl)-1-but-1,3-enesulfonamide*. A solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-chlorobenzyl)-methanesulfonamide (Example 1, step b) (500mg, 1.56mmol) in THF (5ml) was cooled to –78°C, 1M potassium *t*-butoxide (3.12ml, 3.12mmol) was added dropwise and the solution was stirred for 1h. A solution of the product from the previous step (358mg, 1.56mmol) was added by means of a cannula and the solution was stirred overnight, allowing it to warm slowly to room temperature. The reaction mixture was partitioned between saturated ammonium chloride solution (20ml) and ethyl acetate (20ml). The organic phase was washed with brine, dried over magnesium sulfate, filtered and the solvent evaporated. Recrystallisation of the residue from ethyl acetate gave the product as a colourless crystalline solid (529mg, 78%).

Step e. (E,E)-N-*allyl*-N-*(4-chlorobenzyl)-4-(1-(dimethylsulfamoyl)-imidazol-4-yl)-1-but-1,3-enesulfonamide*. A solution of the product from the previous step (446mg, 1.04mmol) in dry dimethylformamide (3.6ml) was cooled in ice. Sodium hydride (60% dispersion in oil) (47mg, 1.18mmol) was added, the cold bath was removed and the mixture was stirred for 25min. The mixture was cooled again in ice, allyl bromide (139µl. 1.61mmol) was added and the solution was stirred overnight at ambient temperature. Water (15ml) was added. The resultant precipitate was collected by filtration and dried in vacuo over phosphorus pentoxide. Recrystallization from ethanol afforded the product as a colourless crystalline solid (411mg, 84%).

Step f. *2-(4-chlorobenzyl)-5-(1-(dimethylsulfamoyl)-imidazol-4-yl)-2,3,3a,4,5,7a-hexahydro-benzo[*d*]isothiazole 1,1-dioxide.* A solution of the product from the previous step in dry degassed toluene (4ml) was heated at 140–145°C in a sealed pressure vessel for 48h. The solvent was evaporated and the residue was recrystallised from ethanol to afford the product a white solid (28mg, 58%).

Step g. A mixture of the product from the previous step (101mg, 0.21mmol), ethanol (1ml) and 2M hydrochloric acid (1ml) was heated at reflux overnight. The solvent was evaporated and the residue purified by flash column chromatography (silica; 1:10:90 ammonia(880)/methanol/dichloromethane). Thus, the title compound (R_f 0.30) was isolated as a white solid (44mg, 58%). The product was a mixture of isomers (6:1) and the ^{1}H NMR spectrum of the major isomer is reported: ^{1}H NMR (300MHz, *d4*-MeOH) 7.60(1H, s), 7.34(4H, m), 6.84(1H, s), 6.32(1H, m), 5.90(1H, m), 4.23(1H, d), 4.07(1H, d), 3.99(1H, m), 3.47(1H, m), 3.33(1H, m), 2.83(2H, m), 2.06(1H, m), 1.91(1H, m). The maleate salt was prepared by lyophilisation of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 52.29, H 4.70, N 8.78%; $C_{21}H_{22}ClN_3O_6S$ requires: C 52.55, H 4.62, N 8.76%.

References

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2. J.L. Kelley, C.A. Miller, E.W. McLean *J. Med. Chem.* 1977, **20**, 721.
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6. M. E. Thompson, *J. Org. Chem.* 1984, **49**, 1700.

The biological activity of the compounds of the examples was measured using the ileal longitudinal muscle, myenteric plexus assay described by Paton and Aboo Zar (*J. Physiol.* 1968, **194**, 13-33). Male Dunkin-Hartley guinea pigs (250-300g) were employed. Briefly, a 50cm portion of ileum proximal to the caecum was removed, after discarding the terminal 20cm. Ileal segments (3cm) were cleaned by passing Krebs-Henseleit buffer containing 3μM mepyramine gently through the ileum using a Pasteur pipette (size: 13.8cm length, 0.65cm diameter). To avoid unnecessary damage to the tissue, Krebs-Henseleit buffer was passed through the ileal segment, while it was lying horizontally on a petri dish. Therefore, the ileum was not over-distended and the buffer flowed through with ease. Each segment was then passed over a Pasteur pipette and the longitudinal muscle layer and adhering myenteric plexus was teased away using moist cotton wool, by stroking tangentially away from the mesenteric attachment. The tissues were suspended in 20ml organ baths containing Krebs-Henseleit buffer at $37 \pm 1°C$ and gassed with $95\%CO_2/5\%O_2$. The tissues were ligated to two parallel stainless steel wires, situated between two platinum electrodes (0.76cm length, 0.06cm diameter). All measurements were recorded isometrically (Grass FTO3 transducer). Following an initial loading tension of 1g, the tissues were stimulated with electrical pulses at a frequency of 0.1Hz and a pulse duration of 0.5msec, as described by Kosterlitz & Watt (*Br. J. Pharmacol.* 1968, 266-276). Initially, the tissues were stimulated at supramaximal (1.3 fold times maximal) voltage for a period of 30 min and then the tissues were washed and re-stimulated. A "sighter dose" of the selective histamine H_3-receptor agonist, R-(α)-methylhistamine (0.3μM) (Arrang *et al. Nature*, 1987, 117-123), was administered. Upon generation of response, the "sighter dose" was removed from the tissues by "washout" (6 washes over 60 min) and during this period the electrical stimulation was switched off. The tissues were then re-stimulated and allowed to stabilise prior to the addition of drug treatments, which were allocated on a randomised block basis to the organ baths. Following the incubation period, a single cumulative E/[A] curve was obtained. The experimental E/[A] curve data was expressed as the percentage inhibition of the peak height of electrically-stimulated contraction. Antagonist affinity values were calculated from the degree of rightward shift of the R-(α)-methylhistamine E/[A] curves using Schild's methods (Arunlakshana & Schild *Br. J.*

Pharmacol. 1959, 48-58). The results are set out in Table 1. Typical variance in this assay is ± 0.15 log units.

Table 1

Example No.	pK_B (functional assay) - ileum
1	8.06
2	6.62
3	7.90
4	6.59
5	8.46
6	7.79
7	8.29
8	7.90
9	6.52
11	7.53
12	7.31
13	7.23
14	6.14
15	8.47
16	7.74
17	7.33
18	6.41
19	6.61

Example No.	pK_B (functional assay) - ileum
20	6.48
21	7.23
22	7.10
23	6.67
24	7.97
25	7.52
26	8.11
27	7.85
28	7.72
29	7.59
30	8.03
31	6.76
32	7.60
33	8.33
34	7.76
35	6.82
36	5.81
37	7.69
38	7.91
39	7.61
41	5.58

Example No.	pK_B (functional assay) - ileum
42	5.68

Histamine H_3 radioligand binding assay - guinea pig ileum

Preparation of membranes

Male Dunkin Hartley guinea pigs (200-300g) were used. The small intestine was rapidly removed (cut ~5cm from caecum and 5cm from stomach) and placed in ice-cold 20mM Hepes-NaOH buffer (pH7.4 at 21±3°C). The tissue was cut into ~10cm segments, flushed through with ice-cold 20mM Hepes-NaOH buffer and placed in a beaker containing fresh buffer at 4°C. 10cm segments of ileum were threaded onto a glass pipette and the longitudinal muscle myenteric plexus was peeled away from the circular muscle using damp cotton-wool. Longitudinal muscle myenteric plexus was immediately placed in ice-cold Viaspan® solution (~100ml for tissue from 3 guinea pigs) and placed in the refrigerator for 24 hours.

Pre-soaked tissue was weighed and minced with scissors. The tissue was then homogenised in Viaspan® using a polytron (Kinematica AG; PT-DA 3020/2TS, 3 x ~1-2s). 50ml of 500mM Tris HCl (pH6.9 at 21±3°C) was added to the tissue and the mixture centrifuged at 39,800 x g for 12 min at 4°C. The supernatant was discarded and rehomogenised in 100ml ice-cold 20mM Hepes-NaOH buffer (pH7.4 at 21±3°C) using a teflon-in-glass homogeniser (setting 10; 3 x). The homogenate was recentrifuged at 39,800 x g and the pellet resuspended in 20mM Hepes-NaOH buffer (pH7.4 at 21±3°C), to a tissue concentration of 50mg.ml^{-1}, using a polytron (Brinkman, PT10, 3 x ~1s).

Incubation conditions

Guinea pig ileum longitudinal muscle myenteric plexus membranes (400µl) were incubated for 165 min at 21 ±3°C in a final volume of 500µl with 20mM Hepes-NaOH buffer containing [^{3}H]-R-α-methylhistamine (50µl; 3nM) and competing compound. Total and non-specific binding of [^{3}H]-R-α-methylhistamine were defined using 50µl of buffer and 50µl of 10µM thioperamide, respectively. The assay was terminated by rapid filtration through Whatman GF/B filters, presoaked (2hr) in 0.1% polyethyleneimine, using a Brandell Cell Harvester. The filters were washed (3 x 3ml) with ice-cold 50mM Tris-HCl (pH6.9 at 21 ±3°C), transferred into scintillation vials, 5ml liquid scintillation cocktail was added and after 4 hours the bound radioactivity was determined by counting (4 min) in a Beckman liquid scintillation counter.

Data analysis

Data are analysed using GraphPad prism and the general equation for a competition curve with variable Hill slope (n_H).

$$Y = \text{Non-specific binding} + \frac{\text{(Total binding - Non-specific binding)}}{1+10^{((\log IC_{50}-X).n_H)}}$$

where

X is the log concentration of competing compound,

Y is the binding obtained at each concentration of X,

pIC_{50} is the concentration of the competitor required to compete for half of the specific binding.

The IC_{50} is converted to the K_I using the Cheng Prusoff equation,

$$K_I = IC_{50}/(1+(L/K_D))$$

where

IC_{50} is the concentration of competitor required to compete for half the specific binding,

L is the radioligand concentration used,

K_D is the equilibrium dissociation constant for the radioligand determined by saturation experiments.

The results are set out in Table 2. Typical variance in this assay is $\pm$ 0.12 log units.

Table 2

Example No.	pK_I (binding assay) - ileum
1	8.07
3	7.99
5	8.73
6	7.90
12	7.22
26	7.99
27	7.93

Histamine H_3 radioligand binding assay - guinea pig cortex

Preparation of membranes

Male Dunkin Hartley guinea pigs (200-300g) were used. The whole brain was removed and immediately placed in ice-cold 20mM Hepes-NaOH buffer (pH7.4 at 21±3°C). The cortex was dissected, weighed and homogenised in ice-cold 20mM Hepes-NaOH buffer (pH7.4 at 21±3°C) (50ml/guinea-pig cortex) using a polytron (Kinematica AG; PT-DA 3020/2TS, 3 x 3s). The homogenate was centrifuged at 100 x g for 5min and the supernatants pooled and stored at 4°C. The pellets were rehomogenised in fresh ice-cold buffer (80ml) and recentrifuged (100 x g for 5min). The supernatants were pooled and pellets rehomogenised and recentrifuged (100 x g for 5min). All supernatants were pooled and centrifuged at 39,800 x g for 12 min at 4°C. The final pellet was resuspended in 20mM Hepes-NaOH buffer (pH7.4 at 21±3°C) to a tissue concentration of 7.5mg.ml^{-1},using a teflon-in-glass homogeniser.

Incubation conditions and data analysis

These were essentially identical to those used for the guinea pig ileum myenteric plexus assay described above, except that the final assay concentration of [^{3}H]-R-α-methylhistamine was 0.1nM. The results are set out in Table 3. Typical variance in this assay is ± 0.12 log units.

Table 3

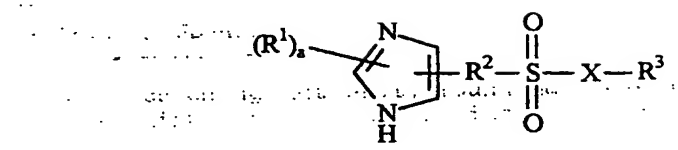
Example No.	pK_i (binding assay) - cortex
1	8.58
2	6.56
3	8.56
4	7.21

Example No.	pK_I (binding assay) - cortex
5	8.58
6	8.30
7	8.54
8	8.37
9	7.35
10	6.13
11	8.14
12	7.85
13	8.05
14	7.09
15	9.05
16	8.95
17	7.66
18	6.85
19	7.71
20	6.90
21	7.92
22	7.54
23	7.32
24	8.25
25	7.73

Example No.	pK_I (binding assay) - cortex
26	8.35
27	9.18
28	8.15
29	8.21
30	8.82
31	6.73
32	8.23
33	9.07
34	7.99
35	7.74
36	6.70
37	8.18
38	8.88
39	8.53
40	4.65
41	5.80
42	5.91

CLAIMS

1. A compound of the formula



(I)

wherein R^1 is selected from C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 alkylthio, carboxy, carboxy(C_1 to C_6)alkyl, formyl, C_1 to C_6 alkylcarbonyl, C_1 to C_6 alkylcarbonylalkoxy, nitro, trihalomethyl, hydroxy, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, aryl, C_1 to C_6 alkylaryl, halo, sulfamoyl and cyano;

R^2 is C_1 to C_{20} hydrocarbylene, in which one or more hydrogen atoms may be replaced by halogen atoms and up to 6 carbon atoms may be replaced by oxygen, nitrogen or sulfur atoms, provided that R^2 does not contain a -O-O- group, and provided also that the atom in R^2 which is linked to the $-SO_2-$ moiety is a carbon atom;

R^3 is hydrogen or C_1 to C_{15} hydrocarbyl, in which one or more hydrogen atoms may be replaced by halogen atoms and up to 3 carbon atoms may be replaced by oxygen, nitrogen or sulfur atoms, provided that R^3 does not contain a -O-O- group;

X is a bond or $-NR^4-$, wherein R^4 is hydrogen or non-aromatic C_1 to C_5 hydrocarbyl (in which one or more hydrogen atoms may be replaced by halogen atoms and up to 2 carbon atoms may be replaced by oxygen, nitrogen or sulfur atoms, provided that R^4 does not contain a -O-O- group), aryl(C_1 to C_3)alkyl or R^4 represents a bond to R^2; and

a is from 0 to 2,

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein a=0.

3. A compound according to claim 1 or claim 2 wherein R^2 is C_1 to C_{15} hydrocarbylene, in which one or more hydrogen atoms may be replaced by halogen

atoms and up to 4 carbon atoms may be replaced by oxygen, nitrogen or sulfur atoms, provided that R^2 does not contain a -O-O- group.

4. A compound according to any preceding claim wherein R^2 is C_1 to C_8 alkylene or alkenylene, optionally substituted by a hydroxyl group, an oxo group, an amino group, or an (C_1 to C_3)alkylamino or dialkylamino group.

5. A compound according to any preceding claim wherein R^3 is hydrogen, cycloalkylalkyl or aryl(C_1 to C_3)alkyl.

6. A compound according to any preceding claim wherein R^4 is hydrogen, C_1 to C_5 alkyl or benzyl.

7. A compound according to any preceding claim wherein X is -NR^4-.

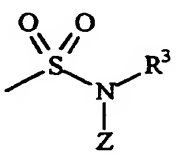
8. A compound according to any of claims 1 to 6 wherein X is a bond.

9. A compound according to any preceding claim, for use in therapy.

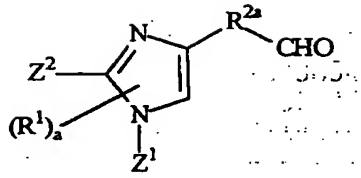
10. A compound which is degraded *in vivo* to yield a compound according to any of claims 1 to 8.

11. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1 to 8, and a physiologically acceptable diluent or carrier.

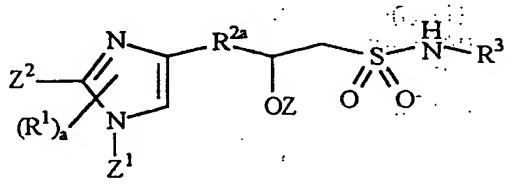
12. A method of making a compound according to claim 1, said method comprising the step of reacting a compound of formula



with a compound of formula

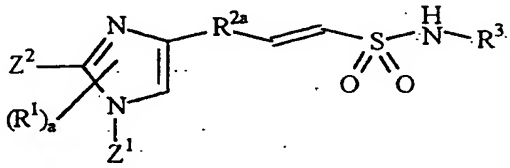


wherein a, R^1 and R^3 are as defined in claim 1, Z is H or a suitable migrating group such as Boc, Z^1 is a protecting group, Z^2 is H or a further protecting group, and R^{2a} is C_1 to C_{18} hydrocarbylene, to yield compounds of the formulae



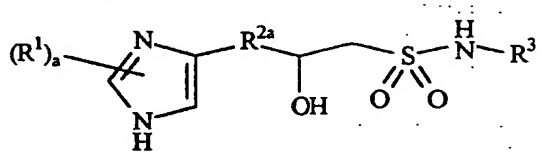
(III)

and/or

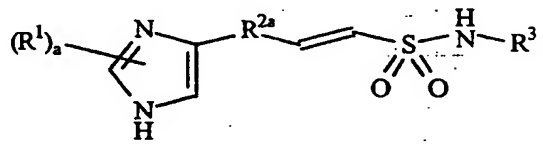


(IV)

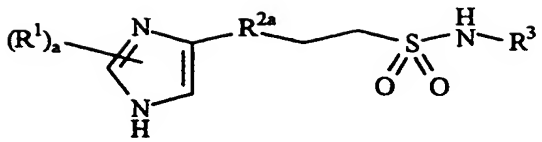
13. A method according to claim 12 wherein a compound of formula III is deprotected to yield a compound of formula



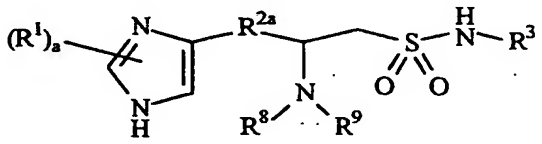
14. A method according to claim 12 wherein either a compound of formula III is reacted with a base and then deprotected, or a compound of formula IV is deprotected to provide a compound of formula



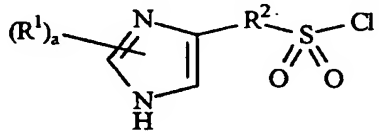
15. A method according to claim 12 wherein either a compound of formula III is reacted with a base, reduced and then deprotected, or a compound of formula IV is reduced and then deprotected to provide a compound of formula



16. A method according to claim 12 wherein a compound of formula IV is reacted with an amine and then deprotected to yield a compound of formula

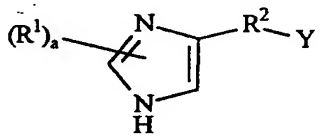


17. A method of making a compound according to claim 1 in which X is -NH-, said method comprising the step of reacting a compound of formula



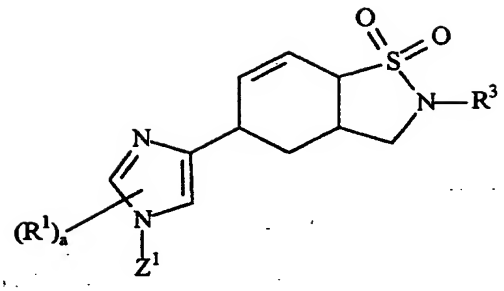
with a compound of formula R^3NH_2 in the presence of a base.

18. A method of making a compound according to claim 1 in which X represents a bond, said method comprising the step of reacting a suitably protected compound of formula



(wherein Y represents a leaving group such as bromide) with a compound of formula R^3SH, followed by oxidation of the resulting thioether.

19. A method according to claim 12 wherein a compound of formula IV, R^{2a} being -CH=CH-, is reacted with sodium hydride, and then with allyl bromide, followed by heating under pressure to form a compound of formula



which may then be deprotected.

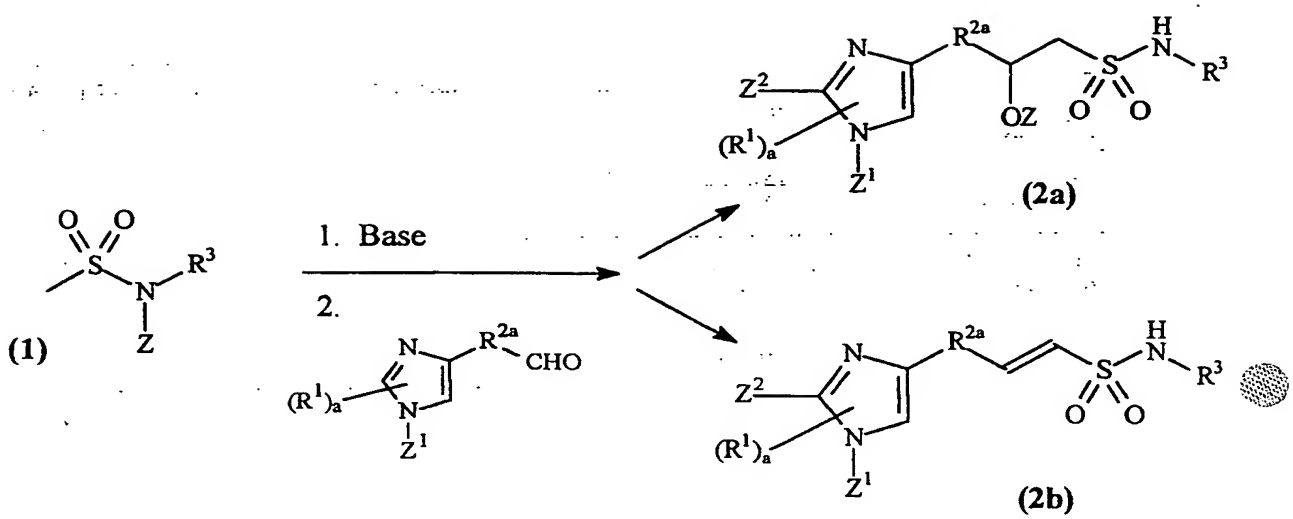


Figure 1

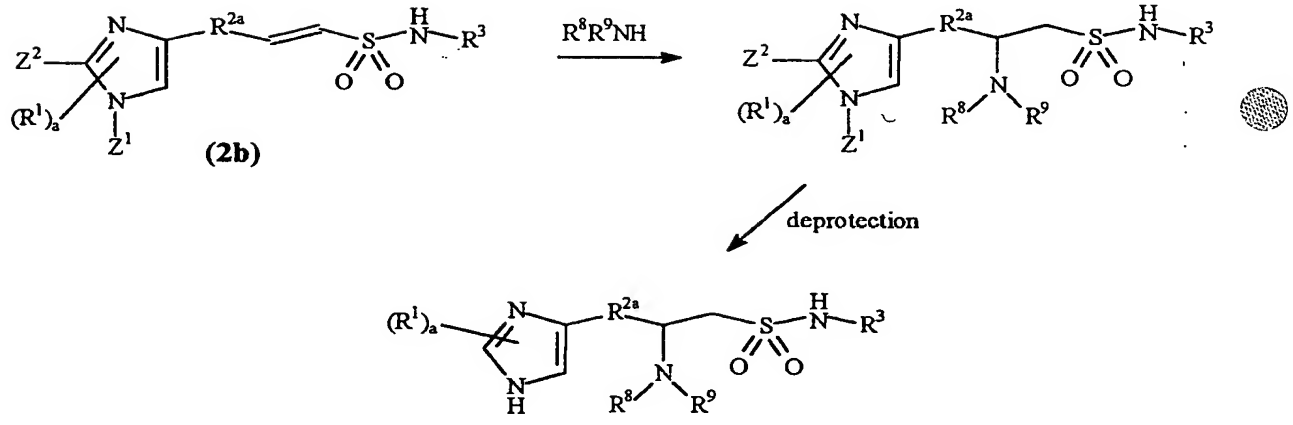


Figure 2

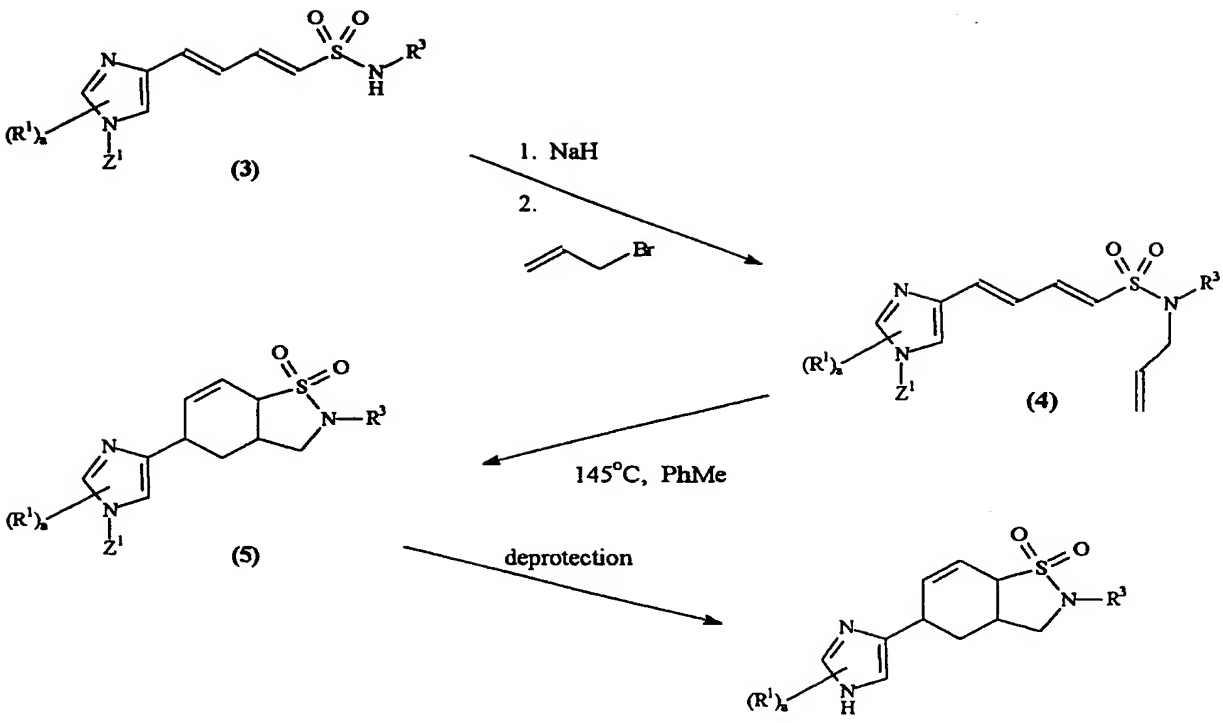


Figure 3

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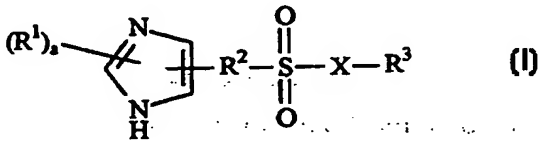

(I)

(57) Abstract

Compounds of formula (I) wherein R^1 is selected from C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 alkylthio, carboxy, carboxy (C_1 to C_6)alkyl, formyl, C_1 to C_6 alkylcarbonyl, C_1 to C_6 alkylcarbonylalkoxy, nitro, trihalomethyl, hydroxy, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, aryl, C_1 to C_6 alkylaryl, halo, sulfamoyl and cyano; R^2 is C_1 to C_{20} hydrocarbylene, in which one or more hydrogen atoms may be replaced by halogen atoms and up to 6 carbon atoms may be replaced by oxygen, nitrogen or sulfur atoms, provided that R^2 does not contain a -O-O- group, and provided also that the atom in R^2 which is linked to the $-SO_2-$ moiety is a carbon atom; R^3 is hydrogen or C_1 to C_{15} hydrocarbyl, in which one or more hydrogen atoms may be replaced by halogen atoms and up to 3 carbon atoms may be replaced by xygen, nitrogen or sulfur atoms, provided that R^3 does not contain a -O-O- group; X is a bond or $-NR^4-$, wherein R^4 is hydrogen or non-aromatic C_1 to C_5 hydrocarbyl (in which one or more hydrogen atoms may be replaced by halogen atoms and up to 2 carbon atoms may be replaced by oxygen, nitrogen or sulfur atoms, provided that R^4 does not contain a -O-O- group), aryl(C_1 to C_3)alkyl or R^4 represents a bond to R^2; and a is from 0 to 2, and their pharmaceutically acceptable salts are useful as histamine H_3 receptor ligands.

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INTERNATIONAL SEARCH REPORT

Interna. _ al Application No
PCT/GB 98/02067

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D233/54 A61K31/415 C07D417/04 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 444 175 A (SHEN T.-Y. ET AL.) 13 May 1969 see example 6 ---	1-4,8,9, 11
X	DE 20 61 489 A (MERCK & CO. INC.) 29 July 1971 see page 20; claim 1; example 22 ---	1,3,5-7, 9,11
X	US 3 682 949 A (SARETT L.H. ET AL.) 8 August 1972 see column 78; example 69 ---	1-3,6,7
X	FR 2 227 869 A (SMITH KLINE & FRENCH LABORATORIES LIMITED) 29 November 1974 see claims 1,2,10; examples 17,18 --- -/--	1-3,7,9, 11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 January 1999	12.02.99

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Interna...al Application No
PCT/GB 98/02067

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 901 908 A (FITZI K. & PFISTER R.) 26 August 1975 see column 13, line 40 - line 44; example 5 see column 17, line 6 - line 10; example 6 see column 18, line 16 - line 19; example 7 see claims 1,5	1,3,8,9, 11
X	GB 1 421 792 C (SMITH KLINE & FRENCH LABORATORIES LIMITED) 21 January 1976 see claims 1,4,16; example 8	1,3,4,8, 9,11
X	VAN DER STELT ET AL.: "Synthesis and pharmacological properties of a series of.alpha.,.alpha.-diaryl-1H-imidazole-2-methanol derivatives" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, CHIMICA THERAPEUTICA, vol. 13, no. 3, May 1978 - June 1978, pages 251-253, XP002080033 see compound 9 see page 253; table I	1-3,8,9, 11
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INTERNATIONAL SEARCH REPORT

Internat...al Application No
PCT/GB 98/02067

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

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Y	WO 93 14070 A (INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE ET AL.) 22 July 1993 cited in the application see claims 1-5,8,27-33; examples 48,49	1-9,11
Y	WO 95 14007 A (SCHERING CORPORATION) 26 May 1995 cited in the application see compound 33, page 34 see claims 1,13,18-23	1-9,11
Y	WO 96 38142 A (GLIATECH, INC.) 5 December 1996 see claims 1,4,7,16-20	1-9,11
P,Y	WO 97 29092 A (JAMES BLACK FOUNDATION LIMITED) 14 August 1997 see claims 1-17	1-9,11

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INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-9, 11-19 (all partially) and 10
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-3 (partially), 4 and 5-18 (partially)

Compounds of formula (I) wherein R2 is hydrocarbylene which "refers to divalent groups consisting of carbon and hydrogen with the two free valencies being on separate atoms".

2. Claims: 1-3 (partially) and 5-18 (partially)

Compounds of formula (I) wherein R2 is hydrocarbylene with "up to 6 carbon atoms [being] replaced by oxygen, nitrogen or sulfur atoms".

3. Claims: 1,2,5,7,9-11 (all partially) and 19

Compounds of formula (I) wherein "R4 represents a bond to R2".

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 1-9, 11-19 (all partially) and 10

An ambiguity arises from the definition of radicals R2, R3 and R4 being "hydrocarbylene" and "hydrocarbyl" respectively in which "one or more hydrogen atoms may be replaced by halogen atoms and up to 6 carbon atoms may be replaced by oxygen, nitrogen or sulfur atoms". In contradiction to the definition of "hydrocarbylene" found on page 5 of the description a "C1-hydrocarbylene" does not have the two valencies on separate atoms. Furthermore a hydroxyl or an amino group are not foreseen as substituents of hydrocarbyl(ene) as e.g. in claim 4, since oxygen, nitrogen and sulfur are defined as replacements of a -CH2- or a =CH- group only, cf. Article 6 PCT.
Claim 10 defines the subject-matter regarding the starting products by a functional expression (leaving in fact open any possibility) instead of indicating the technical measures (structural elements) required to achieve the desired result and thus contravenes Article 6 PCT.

The definition of the compounds of formula (I) is too general and/or encompasses too broad a range of different chemical groups, only partly supported by examples given in the description. The vast number of theoretically conceivable compounds resulting from a claim 1 drafted in such an ambiguous way precludes a comprehensive search.
The search was performed on the basis of those claims which are clear and concise and in the light of the examples and reasonable generalisations thereof and includes compounds having therapeutical activities.

Despite the above limitation the search revealed too many relevant documents so that the search report shall not be considered complete, since the search had to be further limited, cf. Articles 6 PCT, 15(4) PCT and Rule 33 PCT, and the PCT International Search Guidelines chapters III-3.6, III-3.7, VIII-2 and X-6.

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